VOL. CLXI, No. 2 FEBRUARY, 1921 No. 587

1820 "A CENTURY OF SERVICE" 1921

THE

AMERICAN JOURNAL OF THE MEDICAL SCIENCES

GEORGE MORRIS PIERSOL, M.D., EDITOR
JOHN H. MUSSER, JR., M.D., ASSOCIATE EDITOR

THE LIBRARY OF CONGRESS SERIAL RECORD
JUL 26 1944

ACUTE PSYCHOSES ARISING DURING THE COURSE OF HEART DISEASE. By DAVID RIESMAN, M.D. 157

WHOOPING-COUGH CONTRACTED AT THE TIME OF BIRTH, WITH REPORT OF TWO CASES. By JOHN PHILLIPS, M.B. 163

EXPERIMENTAL STUDIES IN DIABETES: SERIES II. THE INTERNAL PANCREATIC FUNCTION IN RELATION TO BODY MASS AND METABOLISM. III. THE EFFECTS OF EXERCISE. By FREDERICK M. ALLEN, M.D. and MARY B. WISHART. . . . 165

RETENTION OF PROTEIN DURING DIET REDUCTION TO RELIEVE THE GLYCOSURIA IN DIABETES MELLITUS. By R. L. FENLON, M.D. 193

THE BACTERIOLOGY OF THE FASTING STOMACH AND DUODENUM: A STUDY BASED ON THE FINDINGS IN THIRTY DOGS. By PETER H. POPPENS, M.D. . 203

LEUKEMIA: TYPE DIAGNOSIS BY OXYDASE METHOD OF BLOOD-STAINING. By GEORGE L. LAMBRIGHT, M.D. 209

THE CURABILITY OF TUBERCULOUS MENINGITIS. By FRANCIS HARBITZ, M.D. . 212

CLASSIFICATION OF GOITER: ANALYSIS OF ONE HUNDRED CASES. By CARRINGTON WILLIAMS, M.D. 223

MULTIPLE FLUID COLLECTIONS IN THE CHEST IN THE COURSE OF THERAPEUTIC PNEUMOTHORAX. By BARNETT P. STIVELMAN, M.D., and JOSEPH ROSENBLATT, M.D. 229

NEPHROLITHOTOMY IN HORSESHOE KIDNEY. By K. P. A. TAYLOR, M.D. . . . 238

INFECTION OF THE KIDNEYS FOLLOWING PROSTATECTOMY. By JOHN W. MARCHILDON, B.S., M.D. F.A.C.S. 243

URINARY ANTISEPSIS: A STUDY OF THE ANTISEPTIC PROPERTIES AND THE RENAL EXCRETION OF 204 ANILIN DYES. By EDWIN C. DAVIS, M.D. . . 251

THE FOURTH VENEREAL DISEASE, ULCERATIVE AND GANGRENOUS BALANOPOSTHITIS: WITH CASE REPORT. By WILLIAM M. DONOVAN, M.D. 267

AMNESIA AFTER CHILDBIRTH. By CHARLES W. BURR, M.D. 271

INTERNATIONAL CONGRESS OF MILITARY MEDICINE AND PHARMACY, ADV. PAGE 26

INDEX TO ADVERTISERS . . . . . ADV. PAGE 18

Contents continued on page 1

OWNERS AND PUBLISHERS
Philadelphia LEA & FEBIGER New York

COPYRIGHT, 1921, BY LEA & FEBIGER. ALL RIGHTS RESERVED. ENTERED AT THE POST-OFFICE AT PHILADELPHIA AS SECOND-CLASS MATTER
PUBLISHED MONTHLY. SUBSCRIPTION, SIX DOLLARS A YEAR, POSTPAID

Gonococcus Glycerol-Vaccine

Stable and Effective

Advantages:

1 - Will not deteriorate. 2 - Free from autolytic products.
3 – In preliminary trials has not produced toxic reactions even in large doses.

The types of cases reported to us as favorably influenced by Gonococcus Glycerol-Vaccine are chronic gonorrheal infections, including gonorrheal rheumatism, epididymitis, prostatitis and posterior urethritis.

Further Information on Request

LEDERLE ANTITOXIN LABORATORIES
511 FIFTH AVENUE NEW YORK

Treat Your Patients at Home

WITH

RABIES VIRUS, LILLY

A Safe Treatment for Administration
by the Patient's Family Physician

THERE is no cure for Rabies, once the symptoms have developed, but the disease may be prevented, during the incubation period, in persons bitten by rabid animals, by prophylactic injections of attenuated rabies virus.

Advantages of Rabies Virus, Lilly

1. A high degree of immunity is established in a short time.
2. The virus is harmless (treatment free from complications, lessened reactions).
3. The virus is uniformly distributed through the vaccine.
4. The patient's time and money are economized.
5. Rabies Virus, Lily, is available for prompt institution of *treatment at home by the family physician.*
6. The dosage is standardized in units (the early doses increasing to a maximum, and this maximum repeated to the end of the treatment).

HOW RABIES VIRUS, LILLY, IS SUPPLIED

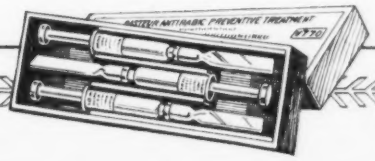
Rabies Virus, Lilly, is supplied in syringe containers, emulsified and ready for use. Your druggist can secure the first three doses from the nearest Lilly depot; the remaining eleven doses will be supplied from Indianapolis, one daily, until the complete treatment of fourteen doses has been supplied.

Write for Booklet on Rabies and Its Treatment

ELI LILLY & COMPANY

INDIANAPOLIS, U. S. A.

NEW YORK CHICAGO ST. LOUIS KANSAS CITY NEW ORLEANS



Hindle American Electrocardiograph

During the past year many of the most important institutions in the country have equipped themselves with the Hindle American Electrocardiograph.

The hospitals now find it necessary to include this apparatus as a valuable aid to their diagnoses, and no examination of the heart can be considered complete without an electrocardiogram.

New institutions should consider the wiring of the wards in making their future plans. Write us for particulars.

A representative list of institutions using our apparatus:

Bureau of Standards, Washington, D. C.
Cornell University Medical School, N. Y.
Johns Hopkins Hospital, Baltimore, Dept. of Medicine.
Medical Dept., U. S. Army (five equipments).
Government of Philippines, Manila, P. I.
Rockefeller Foundation, Brazil.
Michael Reese Hospital, Chicago.
Western Reserve University, Cleveland.
New York Hospital, N. Y.
Rockefeller Institute, N. Y.
Jefferson Medical College, Phila.
Bellevue Medical College, N. Y. City, etc.

MANUFACTURED BY

Charles F. Hindle

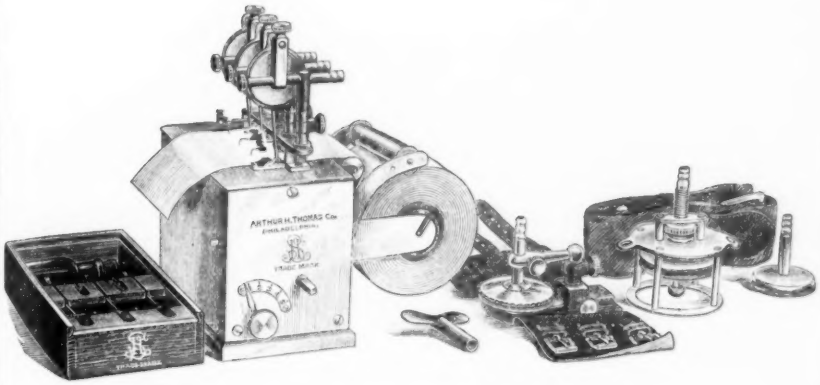
MAIN OFFICE AND FACTORY

(Formerly of 106 E. 126th St. New York City)

OSSINING, N. Y.

JAQUET
PORTABLE POLYGRAPH

THE TEST
IN OUR STOCK FOR IMMEDIATE SHIPMENT
OF SERVICE



No. 43176 Jaquet Portable Polygraph, Complete Outfit

This new model Jaquet Polygraph is an instrument of great precision and convenience and is undoubtedly the most sensitive of all the mechanical devices for the graphic study of the circulation. The instrument records three simultaneous tracings, *i. e.*, the radial pulse, the apex beat and one other, such as the carotid, jugular, etc., in addition to the time tracing. Either smoked paper or ink tracings may be taken, each instrument being furnished with writing pens for both methods. Tracings may be made of any desired length from a continuous roll of paper and at any speed from 1 cm. to 5 cm. per second. The clockwork will run for 25 minutes at the lowest speed of 1 cm. per second. This clockwork is of the highest precision, the workmanship and finish being such as are embodied in no other instrument for similar purpose. The regular equipment consists of cuff for radial pulse, cardiograph for apex beat and a receiving tambour suitable for either the jugular vein or the carotid artery.

43176. Portable Polygraph, Jaquet, as above described, complete outfit consisting of polygraph with sphygmograph for radial pulse, cardiograph for apex beat, receiving tambour for carotid or jugular and one roll each of glazed and smoked paper **$204.00**

Prices subject to change without notice

ARTHUR H. THOMAS COMPANY

WHOLESALE, RETAIL AND EXPORT MERCHANTS

LABORATORY APPARATUS AND REAGENTS

WEST WASHINGTON SQUARE **PHILADELPHIA, U. S. A.**

RADIUM

TO Physicians and Hospitals we offer Radium element of highest purity salts in form of Bromide or Sulphate. Sales are based upon certified measurement by the United States Bureau of Standards, Washington, D. C.

American mining properties owned by this Corporation supply our Radium-bearing ore and we control every mining, refining and laboratory operation in the production of our Radium. This gives us complete knowledge of the purity which we guarantee.

We manufacture Needles, Applicators, Screens and special equipment for the therapeutic use of Radium.

THE

Radio Chemical Corporation

58 PINE STREET, NEW YORK

Telephone, John 3141

Plant and Laboratories
ORANGE, N. J.

Mines
COLORADO, UTAH

Gastron

"arrives"

For a long time GASTRON was "the thing beyond," the product-to-be—an extract of the entire stomach glands, alcohol-free. The idea that this would be of great interest and importance to the physician was persistent.

Now GASTRON, the reality, actually representative of the gastric gland tissue juice in active principles, in complex properties—obtained by acid-aqueous-extraction—has "arrived," through actual clinical trial, as a reliable and efficient resource in dealing with disorders of gastric function.

N. B.—Gastron contains no sugar.

Fairchild Bros. & Foster
New York

We are producing an

Arsphenamine *and a* Neoarsphenamine

than which no better products are made anywhere in the world

Recent studies carried on in the U.S.P.H.S. Laboratories at Washington comparing the toxicity of the American and Foreign Arsphenamines and Neoarsphenamines demonstrate that the American products exhibit a lower toxicity.

Analogous studies made in our own laboratories give similar results.

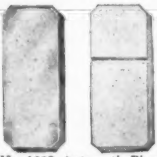
Our Neoarsphenamine is rapidly soluble and may be administered in 5 c.c. of water. It is splendidly tolerated and produces admirable clinical and serological results.

DERMATOLOGICAL RESEARCH LABORATORIES
1720-22 Lombard Street and 1713-15-17-19-21-23 Naudain Street
PHILADELPHIA

DARE
HEMOGLOBINOMETERS

No. 1003
Candle and Electric Illumination. Attached to any Lamp Socket.
$40.00

Examination of blood undiluted gives no chance for error, and makes for certainty in diagnosis.



No. 1008, Automatic Pipet, **$1.50**

Standard Equipment with Mayo Clinic, Army Medical School, U. S. Army, U. S. Public Health Service, etc.

WRITE TODAY FOR BOOKLET

For sale by leading supply houses

No. 1007—Candle illumination
$30.00

RIEKER INSTRUMENT COMPANY
1919 FAIRMOUNT AVENUE PHILADELPHIA, PA.

SPENCER SUPREMACY
IN MICROTOME BUILDING

IS SHOWN IN

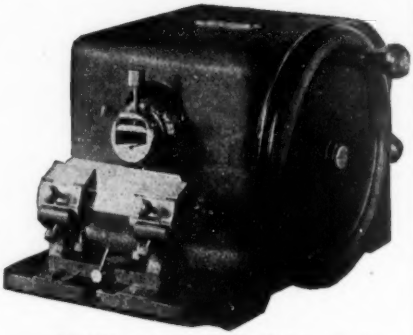
Rotary Microtome No. 820

The only Rotary Microtome ever built with an

INCLINE-PLANE-FEED

It completely overcomes all the inaccuracies usually encountered in other rotary microtomes, due to the up-and-down movement of the object.

In this microtome the feed and the up-and-down movement are **ENTIRELY INDEPENDENT.**



SPENCER ROTARY MICROTOME No. 820

ITS SUPREMACY

has gained for it an international reputation for perfection. It is in use in every important laboratory in the United States and in leading laboratories throughout the world. Prompt deliveries now.

SPENCER BUFFALO U.S.A.

SPENCER LENS COMPANY
MANUFACTURERS
Microscopes, Microtomes, Delineascopes
BUFFALO, N. Y.

SPENCER BUFFALO U.S.A.

Cash Paid for Books Highest prices paid for single medical books and complete libraries. Send us list showing author, title and date of publication.

POWNER'S BOOK STORE, 26 E. Van Buren Street, Chicago, Ill.

Stores in CHICAGO, CLEVELAND and LOS ANGELES

CASTLE AUTOCLAVES

New Pattern

THE sterilizing chamber is made with a seamless drawn copper shell—extra heavy to insure years of service. All riveting and soldering on the bottom and sides has been eliminated. Cover made of high-grade bronze

Offered now in the following sizes:

No. 461-A 8 x 12″
No. 471-A 11 x 24″
No. 481-A 14 x 26″

These autoclaves all have the cover hinged and are supplied complete with high-grade thermometer, safety valve and steam gauge. Gas, electric or oil heating.

Specify Castle Autoclaves when ordering through your supply house. Literature on request.

Wilmot Castle Company

1160 University Ave., ROCHESTER, N. Y.

Makers of the largest line of Sterilizers for laboratories, physicians, dentists and hospitals

HEALTH FOOD COMPANY

RETAIL DEPARTMENT, 27 LEXINGTON AVENUE, NEW YORK CITY

Established 1874 *Manufacturers of* **By FRANK FULLER, M.D.**

SIXTY-FIVE VARIETIES OF FOOD

Our Diabetic foods range from *absolutely starchless* Diabetic Casein Flour, Alpha Cracker, Almond Flour, Soy Bean and Soy Bean Flour to Proto Puffs, 3.26 per cent.—Pure Washed Gluten Flour, 3.77 per cent.—Proto Soy Wafers, 10.53 per cent., and a list of other foods *up to the full starch tolerance diet.*

"A Gluten Flour is prepared especially for the use of Diabetic patients by the NEW YORK HEALTH FOOD COMPANY, it has been used in a number of cases under the author's observation and has proved extremely satisfactory."

"A diet under which nutrition, strength and endurance, either increase or are well maintained although the urine may contain sugar in more or less proportion is preferable to a diet which reduces the amount of sugar but under which the general condition deteriorates." AUSTIN FLINT, M.D.

"It is evident that a single dietary scheme does not suit these different forms and stages of the disease", Diabetes.

"Table 5, Female, aged thirty-five—had had diabetes for several years—had a gangrenous ulcer the size of a palm. Acetonuria and diaceturia appeared remaining without disappearing until a mixed diet of 2 gms. of GLUTEN Bread and 3000 gms. of greens was begun. The gangrenous ulcer healed entirely. Patient is constantly sugar-free. She now gets Gluten bread (with 20% of carbohydrate) per day".
MARIUS LAURITZEN, M.D., University of Copenhagen.

Now Ready for Delivery

HANDY MODEL

Sanborn Metabolism Apparatus

Its light weight and simple technic commend it for use at the bedside in the patient's home.

Its accuracy in determination of the metabolic rate satisfies the most critical clinician.

Comparative tests carried out in the metabolism clinic of one of Boston's largest hospitals, show the Handy Model to be:

DEPENDABLE IN DETERMINATIONS

SIMPLE IN OPERATION

COMFORTABLE FOR THE PATIENT

No intricate computations; nothing to get out of order; no rubber pressure bag; no pressure gage; operating cost negligible; reasonable in price.

Metabolic rate determined by volumetric measurement of oxygen consumed by patient; no gas analysis necessary.

Weighs less than 20 pounds, complete with oxygen tank and convenient carrying case.

Literature and complete information sent free on request.

SANBORN COMPANY

Makers of Scientific Instruments

1048 Commonwealth Ave., : : Boston 47, Mass.

HYCLORITE
CONCENTRATED
SODIUM
HYPOCHLORITE

A Chlorine Antiseptic of Remarkable Stability

HYCLORITE has seven times the strength of Dakin's solution, yet has an alkalinity of only one-sixth of 1%, which makes it practically non-irritating to normal tissue.

It possesses a uniform hypochlorite strength (Na O Cl 4.05%) but, unlike other hypochlorite solutions, has remarkable keeping qualities. No testing is needed in making a Dakin Sol. It is merely diluted with water to desired strength.

Hyclorite does not inhibit leukocytosis and phagocytosis. It has a rapid solvent action on necrotic tissue, produces lymph flow and promotes prompt healing.

Hyclorite is used full strength or diluted to suit the case. In proper dilution, Hyclorite is isotonic. Effective in dilutions as high as 1-2000, it is very economical, and is efficient in all conditions where the use of a hypochlorite antiseptic is indicated.

Accepted by the A. M. A. Council on Pharmacy and Chemistry (N. N. R.)

Write for Sample and Literature to

BETHLEHEM LABORATORIES, Inc.
BETHLEHEM, PA.

Manufactured by
General Laboratories
Madison, Wis.

For
Bethlehem Laboratories, Inc.
Distributors

CONTENTS

ORIGINAL ARTICLES

Acute Psychoses Arising during the Course of Heart Disease 157

By David Riesman, M.D., Professor of Clinical Medicine in the University of Pennsylvania, Philadelphia.

Whooping-cough Contracted at the Time of Birth, with Report of Two Cases 163

By John Phillips, M.B., Cleveland, Ohio.

Experimental Studies in Diabetes: Series II. The Internal Pancreatic Function in Relation to Body Mass and Metabolism. III. The Effects of Exercise 165

By Frederick M. Allen, M.D., and Mary B. Wishart, New York.

Retention of Protein during Diet Reduction to Relieve the Glycosuria in Diabetes Mellitus 193

By R. L. Fenlon, M.D., Iowa City, Iowa.

The Bacteriology of the Fasting Stomach and Duodenum: An Experimental Study Based on the Findings in Thirty Dogs 203

By Peter H. Poppens, M.D., Chicago, Ill.

Leukemia: Type Diagnosis by Oxydase Method of Blood-staining . 209

By George L. Lambright, M.D., Cleveland, Ohio.

The Curability of Tuberculous Meningitis 212

By Francis Harbitz, M.D., Professor of Pathology in the University of Christiana, Norway.

Classification of Goiter: An Analysis of One Hundred Cases 223

By Carrington Williams, M.D., Assistant Surgeon, St. Luke's Hospital, Richmond, Va.

Multiple Fluid Collections in the Chest in the Course of Therapeutic Pneumothorax 229

By Barnett P. Stivelman, M.D., and Joseph Rosenblatt, M.D., Bedford Hills, N. Y.

(*Contents continued on page 12*)

FOR **DIABETICS**

CELLU FLOUR

A non-nutritive flour for filling out reduced diets

27 oz. Bags $2.50 postpaid

Larger quantities at lower rates—Recipes furnished

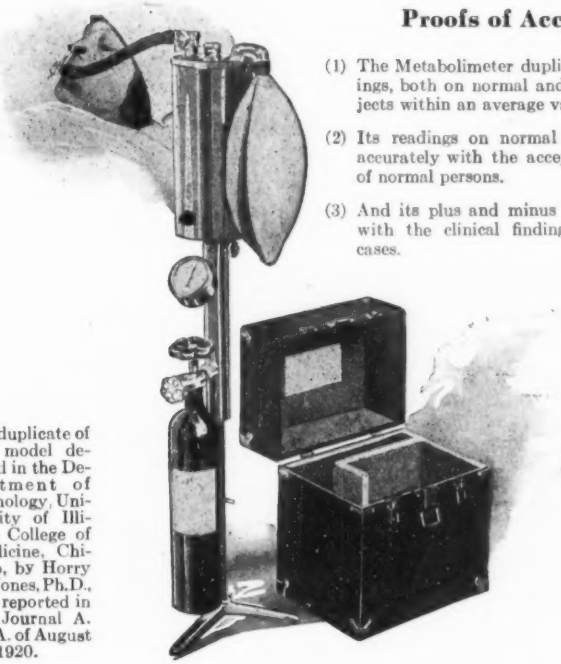
DIETETIC CELLULOSE COMPANY, 2557 W. Chicago Ave., Chicago, Ill.

The New METABOLIMETER

(Pronounced "ME-TA-BO-LIM'-E-TER")

Designed for bedside studies in

BASAL METABOLISM



A duplicate of the model devised in the Department of Pathology, University of Illinois College of Medicine, Chicago, by Horry M. Jones, Ph.D., and reported in the Journal A. M. A. of August 21, 1920.

Proofs of Accuracy

(1) The Metabolimeter duplicates its own readings, both on normal and pathological subjects within an average variation of 2 %.

(2) Its readings on normal subjects compare accurately with the accepted average rates of normal persons.

(3) And its plus and minus readings check up with the clinical findings in pathological cases.

We know of no other proof to furnish the clinician regarding the accuracy of the Metabolimeter. Each instrument carries the maker's guarantee of accuracy.

Advantages of the Metabolimeter

(1) Reads directly in terms of rate of metabolism,

(2) Without the use of logarithms or other calculations, and

(3) Without expensive and time-wasting gas analyses.

(4) Operates with extreme simplicity and consistent accuracy.

(5) Without dyspnea or discomfort to patient.

(6) Requires no special installation for outside air supply, or electrical connection.

(7) Weight 14 lbs.; size of carrying case 13 x 7 x 10 inches.

(8) Cost of operating about three cents per test.

(9) Patient in contact with apparatus about 4 minutes.

Write for a list of leading institutions and internists who depend absolutely on its accuracy in the diagnosis of their borderline cases

DEPT. K

MIDDLEWEST LABORATORIES CO., 1655 N. Sawyer Ave., CHICAGO, ILL.

Makers of Scientific Apparatus

CONTENTS—(*Continued*)

Nephrolithotomy in Horseshoe Kidney 238
By K. P. A. Taylor, M.D., Surgical Service of John B. Deaver, M.D., University of Pennsylvania Hospital, Philadelphia.

Infection of the Kidneys following Prostatectomy 243
By John W. Marchildon, B.S., M.D., F.A.C.S., Genito-urinary Surgeon to the Alexian Brothers' Hospital; Assistant Professor, St. Louis University School of Medicine.

Urinary Antisepsis: A Study of the Antiseptic Properties and the Renal Excretion of 204 Anilin Dyes 251
By Edwin G. Davis, M.D., Omaha, Neb.

The Fourth Venereal Disease, Ulcerative and Gangrenous Balanoposthitis: with Case Report 267
By William M. Donovan, M.D., Instructor in Clinical Medicine, University of Wisconsin Medical School, Madison, Wis.

Amnesia after Childbirth 271
By Charles W. Burr, M.D., Professor of Mental Diseases in the University of Pennsylvania.

REVIEWS

Treatment of Gonorrhea. By Norman Lumb, O.B.E. 279
Public Health and Hygiene. In Contributions by Eminent Authors. Edited by William Hallock Park, M.D. 279
Outlines of Internal Medicine for the Use of Nurses and Junior Medical Students. By Clifford Bailey Farr, A.M., M.D. 280
The New Physiology in Surgical and General Practice. By A. Rendle Short, M.D., B.S., B.Sc. (Lond.), F.R.C.S. (Eng.) 281
Diabetes. By Philip Horowitz, M.D. 282
The Medical Clinics of North America 282
Die Tierischen Parasiten des Menschen. By Dr. Max Braun and Dr. Otto Siefert 283
A Treatise on Materia Medica and Therapeutics, Including Pharmacy, Dispensing Pharmacology and Administration of Drugs. By the late Rakhaldas Ghosh 284

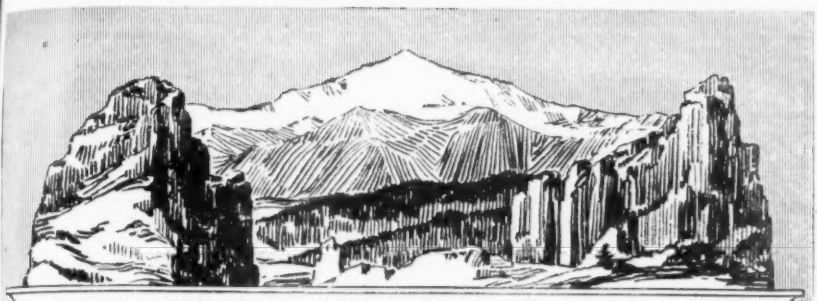
(*Contents continued on page 14*)

Trade Mark Registered.
Gluten Flour
40% GLUTEN
Guaranteed to comply in all respects to standard requirements of U. S. Dept. of Agriculture.
Manufactured by
FARWELL & RHINES
Watertown, N. Y.

SALIPYRIN
"RIEDEL"

"THIS compound possesses the properties of both antipyrine and salicylic acid and combines the analgesic power of the one with the antirheumatic action of the other. It has been used with good results in sciatica, rheumatic fever, chronic rheumatism, influenza, pleurisy, dysmenorrhea, etc."—(*New and Nonofficial Remedies, 1920, American Medical Association.*)

Riedel & Co., Inc.
Bush Terminal Bldg. No. 5, Brooklyn, New York City



RADIUM

TUBULAR APPLICATORS—NEEDLE APPLICATORS—FLAT APPLICATORS
and APPLICATORS *of* SPECIAL DESIGN

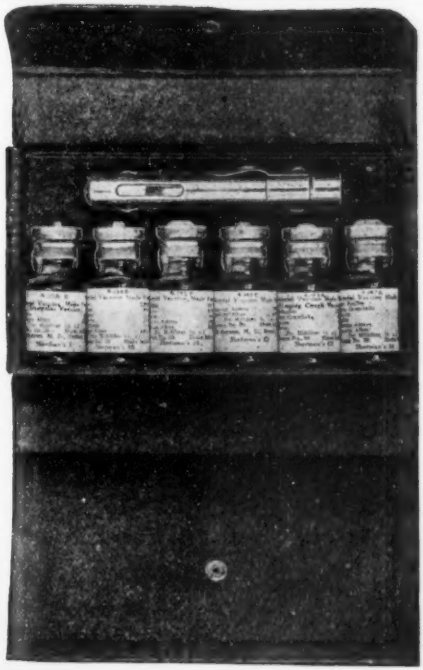
COMPLETE INSTALLATIONS *of* EMANATION APPARATUS

Sold on Basis of U. S. Bureau of Standards Certificate

Correspondence invited by our Physical, Chemical and Medical Departments

THE RADIUM COMPANY OF COLORADO, INC.
Main Office and Reduction Works—DENVER, COLORADO, U. S. A.

BRANCH OFFICES
108 N. State Street, Chicago
50 Union Square, New York
LONDON
PARIS



SHERMAN'S VACCINE CASE

The best immunizing response in Pneumonia is obtained during the first twenty-four hours after the initial chill. Every hour being vitally important, successful immunologists make inoculations in Respiratory Infections at their first call.

Be prepared; carry an assortment of Sherman's Polyvalent Vaccines and self-sterilizing syringe in this convenient case.

Your dealer will be pleased to supply you.

G. H. Sherman, M. D.
DETROIT - - MICHIGAN

Largest Producer of Stock and Autogenous Vaccines

Electric Ionization: A Practical Introduction to its Use in Medicine and Surgery. By A. R. Friel, M.A., M.D. (Dub.), F.R.C.S.I. . . . 284
The X-ray Atlas of the Systemic Arteries of the Body. By H. C. Orrin, O.B.E., F.R.C.S. (Edin.) 285
A Short History of Nursing. From the Earliest Times to the Present Day. By Lavinia L. Dock, R.N., and Isabel Maitland Stewart, A.M., R.N. 285
Handbook of Diseases of the Nose, Throat and Ear. For Students and Practitioners. By W. S. Syme, M.D., F.R.F.P. and S.G., F.R.S.E. 286
Some Conclusions on Cancer. By Charles Creighton, M.D. 286
Manual of Pediatrics. For Students and Doctors. By Dr. Walter Birk 287
Plastic Surgery of the Face. By H. D. Gillies, C.B.E., F.R.C.S. . . 288
Diseases of the Intestine and Lower Alimentary Tract. By Anthony Bassler, M.D. 289
A Practical Medical Dictionary. By Thomas Lathrop Stedman, A.M., M.D. 290

PROGRESS OF MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

W. S. THAYER, M.D., ROGER S. MORRIS, M.D.,

AND

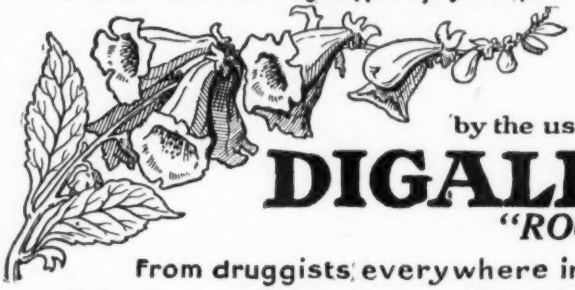
THOMAS ORDWAY, M.D.

The Heart and its Rhythm in Acute Rheumatism 291
Cerebrospinal Fever 292
Diffuse Adenomatosis of the Thyroid Gland 292
Metabolism in Tuberculosis 293

(*Contents continued on page 16*)

DIGITALIS MEDICATION ORALLY-INTRAVENOUSLY OR INTRAMUSCULARLY

is obtained in full degree, promptly and potently



by the use of

DIGALEN

"ROCHE"

From druggists everywhere in

VIALS AMPULS TABLETS

and **HYPODERMIC TABLETS.**

Free Trial Supply and Literature from THE HOFFMANN-LA ROCHE CHEMICAL WORKS ~ NEW YORK

BACILLUS ACIDOPHILUS

Bacid

PREPARATIONS

TABLETS—CAPSULES—LIQUID CULTURES

INTRODUCE

the *Bacillus Acidophilus* which is an organism *of* high acid producing (antiputrefactive) qualities whose

Normal Habitat is the Human Intestine

To ensure a sufficiency *of* this natural defensive organism, when depletion or extinction occurs from any cause whatever, we now offer this

Bacillus Acidophilus in Bacid Preparations as a **new therapeutic agent**

LITERATURE—BIBLIOGRAPHY—ON REQUEST

Guaranteed and Manufactured ONLY by

The Arlington Chemical Company

YONKERS, N. Y.

Standard Product in Heart Cases

Digitan introduced as

Digipuratum

Physiologically Standardized Digitannoids

This product, first introduced as Digipuratum, is manufactured under license from the Federal Trade Commission and carefully standardized according to the original tests

RAPID AND RELIABLE IN ACTION. UNIFORM IN STRENGTH

Supplied in Powder and 1½ grain Tablets

1½ grains powder or 1 tablet Digitan equal to 1½ grains strongly active digitalis leaves = 8 frog units

MERCK & CO. - - NEW YORK and ST. LOUIS

CONTENTS—(*Continued*)

SURGERY

UNDER THE CHARGE OF

T. TURNER THOMAS, M.D.

The Treatment of Chronic Empyema 294
Roentgenographic Appearance, Diagnosis and Pathology of Some Obscure Cases of Bone Lesions 294
The Treatment of Chronic Empyema 295

PEDIATRICS

UNDER THE CHARGE OF

THOMPSON S. WESTCOTT, M.D., AND ALVIN E. SIEGEL, M.D.

An Unusual Case of Cretinism 297
Some Remarks on Cranial Sinus Thrombosis in Children 297
Fluid Injections in Dehydrated Infants 298
The Value of Luetin in an Out-patient Department 298
The Diagnosis and Treatment of Congenital Pyloric Stenosis 299
Intussusception in Infants 299
The Influence of Epidemic Poliomyelitis upon the Susceptibility to and the Symptomatology of Other Contagious Diseases 300
Biological Study of the Hemolytic Streptococcus from the Throats of Patients Suffering with Scarlet Fever 301
The Effect of Intravenous Injections of Calcium in Tetany, and the Influence of Cod-liver Oil and Phosphorus in the Retention of Calcium in the Blood 301

OBSTETRICS

UNDER THE CHARGE OF

EDWARD P. DAVIS, A.M., M.D.

The Diagnosis of Early Ectopic Pregnancy 302

(*Contents continued on page 18*)

ORIGINATION BEGETS IMITATION

Electrically Lighted Surgical Instruments

BE SURE OF OUR EXACT NAME

Twenty years in the manufacture of electrically lighted surgical instruments, if it has not brought perfection in instrument construction, at least has kept the Electro Surgical Instrument Company abreast of the advances made by leading specialists of the medical and surgical profession.

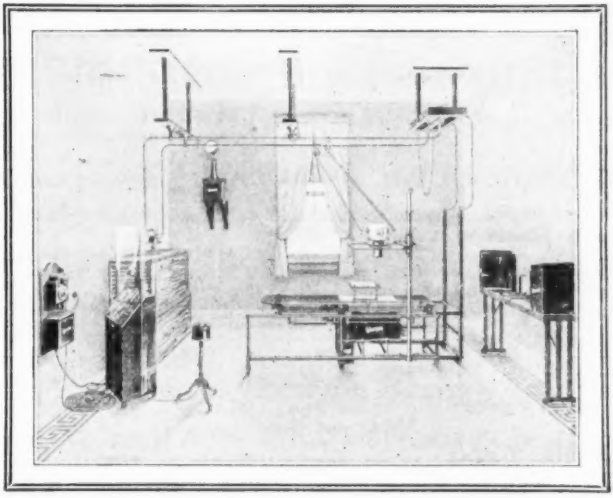
So it is that instruments stamped "E. S. I. Co." speak of the accomplishments of the noted men whose suggestions are embodied in their construction and a service of maintenance possible only in instruments of our manufacture.

Users of instruments stamped "E. S. I. Co." are certain sharers in this service.

Illustrated Catalogue Sent Upon Request

ELECTRO SURGICAL INSTRUMENT CO.

ROCHESTER, N.Y.



Sustained Quality

THE reward of conscientious manufacturing effort is never obscure—it is an ultimate realization.

The reputation enjoyed by a manufacturer today is in the great majority of instances, the culmination of years of close adherence to a high standard.

The Victor Trade Mark on X-Ray and Electro-Physiotherapy Apparatus is universally recognized today as the symbol of quality—in materials, workmanship, design and performance.

A Victor announcement of some new development is accepted by the initiated at face value, for they know that conservatism prevails in the descriptive literature and that the product is offered the profession only after the best engineering skill has approved it.

Add to this the most comprehensive service organization of trained men specializing in this field, extending a personalized service to the user of Victor apparatus, then you have the predominant reasons for the prevalence of Victor installations.

Victor X-Ray Corporation

General Offices and Factory:

Jackson Blvd. at Robey St. Chicago

Sales Offices and Service Stations in all principal cities

GYNECOLOGY

UNDER THE CHARGE OF

JOHN G. CLARK, M.D., AND FRANK B. BLOCK, M.D.

Radium Treatment of Menorrhagia 305
Ovarian Therapy 306
Ovarian Transplantation 307

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

OSKAR KLOTZ, M.D., C.M., AND DEWAYNE G. RICHEY, B.S., M.D.

A Study of the Oxidase Reaction with A-Naphthol and Paraphenylendiamine Tumors 308
The Peroxide Reaction in Three Cases of Multiple Myeloma of the Bones with Remarks Concerning the Nosological Position of these Tumors 309
The Biliary Factor in Liver Lesions 309
A Rapid Method of Pneumococcus Typing 310

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

MILTON J. ROSENAU, M.D., AND GEORGE W. McCOY, M.D.

Masked Juvenile Tuberculosis 311
Saliva-borne Infections: Their Transmission through Eating Utensils . 311
Fatigue and Efficiency of Smokers in a Strenuous Mental Occupation . 312

INDEX TO ADVERTISERS

A WORD TO OUR SUBSCRIBERS—these advertising pages are *clean;* no medical journal sets a higher standard. Only ethical products, and of the highest quality, can gain admittance to these columns. We believe that you can place absolute confidence, as do we, in the firms listed below, all among the leaders in their fields. In writing them, mentioning THE JOURNAL would be appreciated.

Apparatus and Instruments (Bacteriological, Diagnostic, Sterilizers, etc.) PAGE

Wilmot Castle Co. 7
Electro Surgical Instr. Co. 16
Chas. F. Hindle. 2
Middlewest Laboratories Co. 11
Precision Ther. and Instr. Co. 22
Rieker Instr. Co. 6
Sanborn Co. 8
Spencer Lens Co. 6
Arthur H. Thomas Co. . . 3

Biologicals, Drugs, Pharmaceutical Supplies, etc.

Arlington Chemical Co. . . 15
Bethlehem Laboratories, Inc. 9
Ciba Co. . . . . 4th Cover
Dermatological Research Laboratories. 5
Diarsenol Co., Inc. 25
Fairchild Bros. & Foster. . 5
Intra Products Co. 19
Hoffmann-LaRoche Chemical Works 14
Lederle Antitoxin Laboratories. . . . . 2d Cover
Eli Lilly & Co. 1
Merck & Co. 15
H. A. Metz Laboratories, Inc. 28
Parke, Davis & Co. 24
Riedel & Co., Inc. 12
Schering & Glatz, Inc. . . . 19
Dr. G. H. Sherman. 13
E. R. Squibb & Sons. 20
United Synthetic Chemical Corporation 29
Winthrop Chemical Co., Inc. 22

Foods, etc.

Dietetic Cellulose Co. 10
Farwell & Rhines. 12
The Fleischmann Co. 27
Health Food Co. 7
Horlick's Malted Milk Co. 29
Lister Bros., Inc. 21
Mellin's Food Co. . . . 4th Cover

Health Resorts

Battle Creek Sanitarium 35
The Homestead (Hot Springs, Va.) 29

Radium

Radio Chemical Corp. . . . 4
Radium Co. of Colorado, Inc. 13

X-Ray Apparatus, Tubes, etc.

Victor *X*-Ray Corp. 17
Waite & Bartlett Mfg. Co. 23

Miscellaneous

American Institute of Medicine. . . . . 3d Cover
Kalak Water Co. 35
Lea & Febiger. 29–34
Charles T. Powner Co. . . . 6
Standard Oil Co. of N. J. 36

Rheumatism—Then and Now

Formerly the complaint "Rheumatism" promptly brought forth a prescription for Salicylates, simple or complex.

Relief, or even cure, was obtained, though sometimes only after fairly prolonged administration.

The constipating, heart-depressant, kidney-irritant and cumulative toxic by-effects were either not fully realized, or passed up as "necessary evils."

Now-a-days, the physician writes "ATOPHAN," happy to be able to do so much better for his patient.

Quicker, cleaner-cut results, markedly devoid of those "it-can't-be-helped" drawbacks.

U. S. A.-Made and Available Everywhere

COMPLETE INFORMATION AND AMPLE TRIAL QUANTITY FROM

SCHERING & GLATZ, INC., 150 Maiden Lane, NEW YORK

BENZYL ALCOHOL—IPCO

This product complies with the N. N. R. standards

It is a VEN sterile solution, 4 per cent. in 2 c.c. of physiologic sodium chlorid solution, and is ready for immediate use

Of 250 VEN Products in IPCO Ampoules, the popular ones are

VEN—Sodium Iodide No. 41, 15 gr.—No. 42, 30 gr.
VEN—Hexamethylenamine No. 23[A], 31 gr.
VEN—Quinine, 7.5 gr.
VEN—Caffeine No. 51[B], 3.75 gr.—No. 51[C], 7.5 gr.
Camphor in Oil or Ether, all doses
Strophanthin, all doses

Intra Products Company

Denver, Colorado

SQUIBB

Research & Biological Laboratories

THYROXIN SQUIBB

The chemically pure, physiologically active constituent of the thyroid gland, introduced by Kendall and made by E. R. SQUIBB & SONS under license of the University of Minnesota. Possesses all the activity of desiccated thyroid and offers the advantage of accuracy in dosage and therapeutic effect. Marketed in tablets of 1/320, 1/160, 1/80, and 1/32 grain each for administration by mouth. Crystalline Thyroxin for intravenous use is supplied in vials of 10 milligrammes to 100 milligrammes.

NOW READY FOR DISTRIBUTION.

SEASONABLE BIOLOGICALS

ANTIPNEUMOCOCCIC SERUM SQUIBB
Type I

DIPHTHERIA ANTITOXIN SQUIBB
(Small in Bulk—Low in Solids)

LEUCOCYTE EXTRACT SQUIBB
(An adjunct to Serum and Vaccine Therapy)

SMALLPOX VACCINE SQUIBB
(In Capillary Tubes)

THROMBOPLASTIN SQUIBB
(Physiologic Hemostatic)
(Local and Hypodermic)

For almost three-quarters of a century this seal has been justly accepted as a guaranty of trustworthiness.

E·R·SQUIBB & SONS, NEW YORK
MANUFACTURING CHEMISTS TO THE MEDICAL PROFESSION SINCE 1858

THE

AMERICAN JOURNAL

OF THE MEDICAL SCIENCES

FEBRUARY, 1921

ORIGINAL ARTICLES.

ACUTE PSYCHOSES ARISING DURING THE COURSE OF HEART DISEASE.[1]

By David Riesman, M.D.,

PROFESSOR OF CLINICAL MEDICINE IN THE UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA.

Acute mental disturbances sometimes appear during the course of heart disease with such startling suddenness as to disconcert the attending physician and to prove a severe shock to the patient's family. The majority of text-books are silent on this subject, yet the condition is one upon which both from the point of view of etiology and of prognosis much light is needed. Dr. Head, in 1901, in a masterly article,[2] called attention to the mental changes accompanying visceral disease, including heart affections; he concerned himself, however, chiefly with hallucinations of sight, sound and smell, and states of mild depression or exaltation, which he analyzed with very keen insight. In keeping with the opinion of the day in which he wrote, he speaks of aortic valve disease, mitral regurgitation and mitral stenosis, but does not mention that great group of cardiac affections in which valvular lesions play a subordinate or negligible part.

It is of course well known that cardiac patients often are depressed and irritable, particularly after decompensation has been established, and sleep, digestion and respiration are in consequence disturbed. The particular state of mind is closely related to the

[1] Read before the Association of American Physicians, Atlantic City, N. J., May 4, 1920.

[2] Brain, 1901, 24, 345.

patient's temperamental make-up and to his philosophy of life. I once had under my care a woman, aged about forty years, with the most hopeless cardiac break, with dropsy, serous effusions, large liver, cyanosis, insomnia and orthopnea, who until her death maintained a perfect sweetness of disposition and a hopefulness of spirit that was greater than any spes phthisica that I have ever witnessed. On the other hand, I have seen patients who when decompensation was far advanced, by their fretfulness and their unreasonable demands, made life miserable for family, doctor and nurse. But while such a mental condition is abnormal it cannot be called a true psychosis. Nor shall I consider among the cardiac psychoses the delirium of acute and subacute septic endocarditis, since that is dependent more upon the infectious toxemia than upon the heart disease as such.

The manifestations of true psychoses are quite varied. Among the more important types are the following:

1. **Hallucinations** of sight and sound, more rarely of smell. These were found by Head[3] to be most frequent in aortic disease. The auditory hallucinations consist chiefly of rhythmic sounds like the tolling of bells or of knocking; the visual usually take the form of the face of a man or woman with dimly outlined body standing at the foot of the bed or stalking slowly across the room. The patients as a rule recognize the hallucinatory character of the sound or vision and are disinclined to speak of it until the physician has gained their confidence. Hirschfelder[4] states that a number of patients admitted having hallucinations after he had assured them that visual hallucinations were not uncommon in their disease and were merely to be regarded as troublesome but not as significant features. All who gave positive answers accurately described the visual hallucination as detailed above.

The hallucinations are to be looked upon as misinterpreted sensations caused either by anemia or by venous stasis of definite brain centers—those connected with sight or hearing—or by circulatory or trophic disturbances in the corresponding peripheral end-organs. They are usually of a transitory character and do not affect the prognosis in any definite manner.

2. The most common cardiac psychosis is a state of *confusion*, in some cases present only as the patient awakens from sleep or is about to go to sleep; in others it is a more or less constant symptom. The patient confuses his surroundings, is disorientated as to time but may become rational when his attention is sufficiently aroused. This mild type of psychosis is common in myocardial cases with auricular fibrillation with or without decompensation. The less the natural sleep the greater the confusion.

[3] Loc. cit.

[4] Diseases of the Heart and Aorta, Philadelphia, 1918, p. 229.

310Hc1
19 Gy 44

3. In some cases, especially in elderly persons suffering with fibroid myocarditis, the mental state is one of *excitation with decided disorientation*. Such a type is illustrated by the following case:

Mrs. F. H. W., aged seventy years, with cardiac hypertrophy and hypertension, dyspnea on exertion and a little edema of the lower limbs, suddenly began to exhibit a state of mental confusion and excitation which was most marked when she awakened from sleep. She would stare excitedly about the room, talk incoherently and try to get out of bed. When engaged in conversation, she answered most questions pertaining to herself quite well, but to those dealing with the day's events or with familiar contemporary history, she gave confused and inappropriate answers. There was no evidence of motor weakness or paralysis; indeed, she seemed surprisingly strong. The urine contained a faint trace of albumin, no casts, no blood, but a very large quantity of urates; its specific gravity ranged from 1012 to 1022.

The prognosis in such cases is not good, death usually following within a few weeks after the onset of the psychosis. The patient may, however, clear up if the myocardial degeneration has not gone too far and if no complications ensue. In the case just mentioned a pneumonia supervened.

In some cases the state of excitement alternates with one of complete apathy and silence—the patient may sit up promptly when the doctor approaches and may stare directly at him, but answers no questions and does not betray by any sign that he understands what is said to him. Such taciturn myocardial patients have to be watched as they may suddenly become agitated, get out of bed, and make powerful muscular efforts that may end in collapse.

4. Perhaps the most interesting, certainly the most startling disturbance arising in diseases of the heart is *acute mania* which may appear with the suddenness of an apoplexy and for a time defy all efforts at control. I have seen it appear under two conditions: in acute pericarditis and in advanced decompensation of myocardial origin. Its occurrence in pericarditis was pointed out long ago by Da Costa. The late F. A. Packard was the first to bring it to my attention when I was his intern in the Philadelphia General Hospital. We had in our ward a woman, Louisa Wilbur, who had an acute fibrinous pericarditis, the cause of which I do not remember. One day without warning she suddenly became wild and maniacal and had to be restrained. She remained in her state of mania until death. This experience impressed upon me the importance of examining for pericarditis all cases of sudden wild delirium or mania.

Mania in the course of myocardial disease is illustrated by the following case: W. M. R., a physician, aged about fifty years, was brought to my office in June, 1914, in a state of extreme shortness of breath and collapse, which had come on while he was cranking a refractory motor car. Examination showed total arhythmia, an

enlarged heart, enlarged liver but no edema of the extremities. Under rest and digitalis the patient improved; the auricular fibrillation, however, was very slow in subsiding. Although he never regained his full strength, he was able to do a little practice until the spring of 1915; then, despite treatment, he began to lose compensation rapidly. At the beginning of June he suddenly started one day to "act like a crazy man," as his wife expressed it. For six consecutive hours he raced around his library table, throwing his hands wildly about and exclaiming: "I am a thief; no I am not. You are a thief; no you are not. I am a liar; no I am not. You are a liar; no you are not." These phrases he repeated over and over without stopping as fast as he could talk for six solid hours. It was only after Dr. H. MacVeigh Brown, with whom I was seeing him, had given three large hypodermic injections of morphin that the man quieted down. For nearly a week, however, he remained in a state of great physical agitation. He talked incessantly, mostly in a facetious vein, but without much coherence. Throughout that time he slept neither night nor day. It was a marvel to all of us how his heart stood the strain. Toward the end of this period another strange thing happened—the urine, which had been very scanty, became greatly augmented, the dropsy disappeared, and the man was able to lie down flat, which he had not done for a long time. He never regained his mind completely and died in stupor six days after the termination of the maniacal episode.

5. **Delusional States.** When delusions occur they usually take a persecutory form and render the patient most unhappy. While mania and mental confusion are not confined to any particular type of heart disease, I have seen delusions of persecution so far only in connection with lesions of the aortic valve. One of the cases was that of a young baker in my wards at the Philadelphia General Hospital, who had aortic stenosis of rheumatic origin. He thought he was being poisoned with gas by enemies in his shop. Under rest the delusion disappeared in a short time.

6. During attacks of Cheyne-Stokes breathing—a common symptom in cardiac disease—there is at times in the dyspneic period a state of mental excitement or delirium which subsides during the apneic period. The seizures of Adams-Stokes disease, which so closely resemble petit-mal, should also be mentioned here.

In considering *the causes of the cardiogenic psychoses* a number of possibilities suggest themselves:

1. The connection may be an accidental one. In an individual of psychopathic make-up the taint may at any time break forth quite independently of the existence of heart disease, although the latter would favor it by impairing the circulation. In asylums for the insane, cases in which the psychopathy is associated with disease of the heart are numerous. These chronic psychiatric cases do not, however, belong here, as this paper concerns itself only with acute manifestations.

2. A probable factor, in some cases at least, is disease of the kidneys, a frequent concomitant of disorders of the circulation. Uremia by itself is quite capable of producing psychoses, either of the maniacal or of the melancholic type. However, I do not believe that the passive congestion of the kidneys in decompensation of the heart, although often considered a true nephritis, is capable of producing a uremic state. As an accessory factor, it cannot be ignored.

3. I have sometimes thought that acidosis may play a part in the production of mental symptoms in cardiac disease. One often finds when the circulation is failing that the urine becomes intensely acid and throws down a heavy pinkish sediment of urates. This is such a constant phenomenon that I look upon it as possessing diagnostic value. It occurs in secondary renal congestion; not in primary nephritis. A study of the subject of acidosis in diseases of the circulation—the blood carbon dioxide, the hydrogen ion concentration, the ketones and other acid bodies—may, in the future, yield valuable information.

4. That drugs and poisons may be a factor is a natural assumption. An amount of alcohol that in otherwise healthy persons might not do any recognizable harm, may in a patient with disordered circulation lead to a psychosis. Some older writers have held digitalis responsible for maniacal and other acute psychopathic outbreaks. Duroziez[5] reported a number of cases of delirium and coma, which he attributed to digitalis medication. H. O. Hall[6] also called attention to delirium and hallucinations during the course of the administration of digitalis. In one case cited by him (p. 490), it would certainly seem as if digitalis had been responsible for a condition of mental depression bordering on melancholia. Babcock (quoted by Hall) noted in two patients a peculiar mental and emotional state that disappeared after the use of digitalis was discontinued. In the one case, that of a woman, with mitral stenosis, the mental disturbance took the form of a sullen moroseness with taciturnity; while the other patient, a man with aortic insufficiency, manifested a mild delirium of a harmless kind.

At the present moment I have under observation a woman with auricular fibrillation, who, after about the third or fourth day, became confused and talkative. She did not seem to know where she was, although on the occasion of my visits she would answer questions rationally. She herself said, both to the nurse and to me, that she thought the dark medicine did not agree with her. The dark medicine was tincture of digitalis, with a very small amount of tincture of belladonna. I thought that she might have a prejudice, so I substituted digipuratum for the tincture of digitalis. But she also objects to that, and I am strongly inclined to stop the administration of digitalis altogether.[7]

[5] Gaz. hebdom., 1874, xi, 780.

[6] Am. Med., 1901, i, 598; Ibid., 1905, ix, p. 489.

[7] This was done but the psychosis continued, so that it is not likely that digitalis had anything to do with it.

While digitalis may in rare instances exert a direct action upon the brain, it is possible that in some cases when overdoses are given, it may, by disturbing the cardiac rhythm through its action on the conducting mechanism, still further impair an already inadequate circulation. On the whole, however, considering the universal use of the drug and the carelessness in dosage, one would expect that if digitalis could cause psychoses they would be much more frequent.

5. Several years ago I had the following experience: Mr. H. B. B., a man in the late fifties, was suffering with cardiovascular disease, with extreme dropsy. I tried digitalis and all other well-known diuretics without result. About that time agurin appeared on the market. I prescribed it and was amazed to find the urine output increased to an enormous degree, with a coincident rapid disappearance of serous effusions and of every trace of dropsy. During the time that the patient was putting out huge quantities of urine (in one day more than 200 ounces), he developed a delirious, incoherent state, which lasted several days and proved most distressing to his devoted family. I attributed it to a swamping of the system with the toxic material that had been held in solution in the dropsical fluid, and which, in order to reach the kidneys, had to return to the general circulation.

6. In cases in which the foregoing factors are lacking, in which the cardiac patient without neuropathic taint, nephritis, acidosis or exogenous intoxication, develops an acute psychosis, we may assume that it is due to some direct disturbance of the cerebral circulation, affecting the higher centers. At times there is probably syphilitic disease of the vessels, but that is not a prerequisite. Dana's hypothesis[8] concerning the part played by the neuronic synapses may help us to understand why, in disturbances of the circulation, alterations may occur in the psyche. Nevertheless, it is still a far cry from hypofunction of the synapses to an understanding of mental exaltation or depression, of hallucinations or of confusional states.

Not much need be said about treatment, which will vary with the type of disturbance found. Maniacal patients often do not respond to morphin or any of its congeners. I have obtained better results with chloral, which I believe to be not so depressive to the heart as it is usually considered.

As regards diagnosis, it is always necessary to bear in mind that acute mania or melancholia may be symptomatic of visceral disease, in particular, of disease of the heart, and that patients so affected are not of necessity subjects for the asylum. The prognosis is governed by the state of the circulation—if the patient's heart holds out his psychosis will disappear.

[8] Jour. Am. Med. Assn., April 24, 1920.

WHOOPING-COUGH CONTRACTED AT THE TIME OF BIRTH, WITH REPORT OF TWO CASES.

By John Phillips, M.B.,
CLEVELAND, OHIO.

Whooping-cough during the first month of infancy is sufficiently rare that the two cases reported below, in which exposure occurred at the time of birth, are of considerable interest. The infection in each of these cases was from the obstetric nurse, who was in the first week of her attack of whooping-cough. Her cough was not of sufficient severity that she considered it necessary to report it to the obstetrician. In the first case reported she assisted, at the time of labor, the regular nurse for twenty-four hours, and then went to the second case, this baby being born three days later. Although her cough grew steadily worse she did not suspect that it was due to whooping-cough. It should be a golden rule that a nurse who has a cough should not take an obstetric case. I believe, too, that pertussis in adults is often unrecognized, and this is accountable in many cases for the spread of the disease. In one year in three different families, I saw six cases of pertussis contracted from nurses who had coughs, which they thought were due to "ordinary colds." The prevalent idea among the laity, and sometimes among physicians and nurses, that adults seldom contract whooping-cough is responsible for lack of quarantine.

The following are the two cases I wish to report:

Case I.—Female, of healthy parents, was born May 28, 1914. The birth was two weeks premature and the weight of the baby was five pounds ten ounces. During the first three days the child lost six ounces, but these were regained by the end of the first week. A steady gain of one ounce a day was recorded until the tenth day, when the infant began to cough. On the eleventh and twelfth days the cough increased in severity, so that it interfered greatly with nursing, and the food was regurgitated. On the fourteenth day after birth the infant began to whoop, the paroxysms steadily increasing in number and severity, so that on the sixteenth day they numbered twenty-two. On the seventeenth day there were twenty-eight, on the eighteenth thirty, on the nineteenth thirty-eight. During the paroxysms the baby became deeply cyanosed and at times it was with great difficulty that breathing was again established. On the morning of the twenty-first day the infant became stuporous and within a few hours sank into coma; the fontanelle became tense and there was a paresis of one side of the face. The breathing assumed the Cheyne-Stokes type, with periods of apnea

lasting forty seconds. The coma deepened and death occurred that evening. No autopsy was permitted, but the cause of death was evidently a cerebral hemorrhage.

Case II.—Female infant was born June 3, 1914, at full term, weight eight pounds fourteen ounces. The obstetric nurse in attendance had assisted as second nurse in the case of the baby in Case I. At that time she was coughing a great deal but had not reported her cough to the obstetrician, as she did not herself suspect that she had whooping-cough. This second baby began to cough on June 11 and whooped on June 15. The disease ran a moderately severe course for six weeks, the number of paroxysms varying from twelve to twenty in twenty-four hours at the height of the disease. When eight weeks old the baby weighed ten pounds four ounces and during the remainder of the first year thrived well, weighing twenty-two pounds when one year old.

Whooping-cough during the first month may be congenital, but the majority of cases are acquired. Cockayne states that Sir Thomas Watson described a case in which the disease was contracted before the patient was born, saying: "My bedmaker's daughter in Cambridge had a child ill with whooping-cough in the house with her during the last weeks of pregnancy and the newcomer whooped the first day he appeared in the world." Rilliet and Barthez, quoted by the same author, mention the case of a newborn child whose mother had had whooping-cough for a month and who had characteristic fits of coughing on the day of its birth. Blache reports a case as congenital in which the baby began to cough six days after birth, the mother having had whooping-cough, and who had contracted the disease from another child. This case may well be regarded as of doubtful congenital origin, as it would be more likely that the disease was contracted at the time of birth.

Cooper Cole has reported a case of whooping-cough in a premature infant. The mother who had developed very severe whooping-cough in the sixth month of pregnancy gave birth to a well-developed eight months' male infant on May 26. On May 29 the baby coughed for the first time. During the next fortnight the temperature ranged from 99° to 100° F. and the cough became more severe and paroxysmal until June 12, seventeen days after birth, when the child had a typical paroxysm ending in a whoop. For three weeks the paroxysms ranged from twelve to twenty-two daily. Recovery took place and at six months the patient was the equal of any other child of that age. The fact that the baby did not whoop until seventeen days after birth might cast some doubt on the congenital character of this case. That the incubation period of whooping-cough may be very short is shown by a case reported by Cockayne. In his case the baby began to cough on the

fifth day after birth, the disease being contracted from his brother, aged three and a half years, who was allowed to lie on the bed the day after birth and kissed both mother and baby. Bouchut has resported one case in which the infant began to cough two days after exposure. Frederici and Gerhart mention the fact that the incubation period of whooping-cough may be as short as two days, the average time in my own experience being ten to twelve days. With such a short incubation period occasionally occurring in whooping-cough considerable doubt would be cast on some of the cases reported as congenital. The writer cared for three mothers who have acquired whooping-cough in the last month of pregnancy without the babies showing any sign of the disease. When infection does occur it must be through the blood as is the case in congenital typhoid fever.

REFERENCES.

Cockayne: Whooping-cough in the First Days of Life, British Jour. Dis. Children, 1913, x, 534.

Watson, Sir Thomas: Watson's Practice of Physic, edited by Henry Hartshorne, 1872, ii, 94.

Blache: Cited by H. Roger, Recherches cliniques sur les maladies de l'enfance, 1883, ii, 382.

Bouchut, E.: Traite pratique des maladies des nouveaux-nés, 1852, p. 415.

Cooper, Cole C. E.: University Toronto Medical Bulletin, I, 45. Abstract, British Jour. Dis. Children, 1913, x, 371.

Rilliet and Barthez: Traite des maladies des enfants, third edition, 1891, p. 747.

EXPERIMENTAL STUDIES IN DIABETES:

SERIES II. THE INTERNAL PANCREATIC FUNCTION IN RELATION TO BODY MASS AND METABOLISM.

III. THE EFFECTS OF EXERCISE.

By Frederick M. Allen, M.D.,

and

Mary B. Wishart,

new york.

(From the Hospital of the Rockefeller Institute for Medical Research, New York.)

The preceding paper dealt particularly with the metabolism of matter, in the form of changes in the food supply and bodily reserves. The present paper is devoted to the metabolism of

energy as affected by exercise. It is recognized that the distinction is imperfect, since the energy of exercise must be furnished by combustion of material, which either demands increased food or causes undernutrition. Nevertheless, there is a difference, since the mere presence of stores of reserve fat was found to alter the assimilation, while exercise represents not only increased metabolism but also metabolism under a special stimulus.

Of the two factors chiefly concerned in carbohydrate combustion, one, the pancreas, was surgically reduced in Paper 1, and the other, the muscles, in Paper 2. Long-continued exercise builds up the muscles in mass and function. Athletes have a higher than average metabolism,[1] and the basal metabolism of a normal dog may fall as much as 16 per cent. in consequence of prolonged cage life.[2] As the dogs used in these experiments had mostly undergone many months of cage life, it is probable that the muscular factor in metabolism was considerably augmented by the exercise, and observations were therefore possible as to how far the development of this factor might compensate for deficiency of the pancreatic factor.

Mention has been made elsewhere[3] of the early clinical work which indicated that exercise aids sugar combustion and diminishes glycosuria in mild diabetes, but is ineffective or even harmful in severe diabetes. Moraczewski[4] found that exercise increased the blood sugar of normal persons and diabetics, while at the same time improved assimilation was manifest by a diminution of glycosuria. Mackenzie[5] found a rise of 0.085 per cent. or less in the blood sugar of fasting totally depancreatized dogs with exercise, and a fall of 0.1 per cent. or less with exercise in depancreatized dogs receiving 200 gm. of meat and bread daily. The exercise periods were twenty to thirty minutes, and apparently irregularities of absorption and diuresis were not excluded as possible causes of the variations.

A preliminary outline of the present investigation and some observations on the application in clinical treatment have already been published.[6] In the experiments here to be described, dogs were exercised under various conditions of fasting, feeding and intravenous glucose injections. The exercise consisted in hard running on a treadmill, driven entirely by the dog, with no measurement of the amount of work done. The animals mostly enjoyed the running, and it was considered sufficient that they were kept going at full speed for the periods specified. The method of discontinuous intravenous injections, described elsewhere,[7] was adopted primarily with a view to the exercise experiments. The exposure of the jugular and other preparations were made some time in advance. Ordinarily, the glucose for each hour was given in the form of three injections, twenty minutes apart. With the dog

ready on the treadmill, catheterization, collection of the first blood sample and injection of the first dose of glucose were performed; next the animal ran for the specified time (generally fifteen minutes); a pause was made for the next blood sample and injection, and running was resumed.

The dogs were allowed water freely except in the experiments with intravenous injections. The volumes taken are omitted from the tables, because no differences in blood sugar were perceptible whether the animals chose to drink nothing or large quantities. Water was not given in the intravenous injection experiments and the animals were generally not thirsty.

The laboratory technic was the same as in the other papers, *i. e.*, Benedict's methods for sugar, the Fleischl-Miescher hemoglobin estimation, etc. The corpuscle volume was determined first in special capillary tubes of 12 cm. length, later in ordinary graduated centrifuge tubes. The blood was usually concentrated by exercise, but some allowances must be made for the limits of error in the methods.

TABLE I.—DOG C3-47. NORMAL. WEIGHT, 15.4 KGM. THE EFFECT OF EXERCISE ON NORMAL FASTING DOG.

Time.	Plasma sugar, per cent.	Hb., per cent.	Urine.		Rectal temperature, °F.
			Volume, c.c.	Glucose, per cent.	
1 hr. before exercise	0.115	112	..	0	101.4
Immediately before exercise	0.117	110	10	0	101.6
After 15 min. exercise	0.135	111	..	..	102.7
After ½ hr. exercise	0.176	111	..	..	104.1
After 1 hr. exercise	0.133	111	4	0	104.6
After resting 2 hrs.	0.139	111	25	0	101.4

TABLE II.—DOG B2-90. NORMAL. WEIGHT, 33 KILOS.

Date, 1915.	Hour.	Plasma sugar, per cent.	Hb., per cent.	Remarks.
Oct. 5	2.45 P.M.	0.111	65	Blood before exercise.
	3.30	0.154	66	After ¾ hr. of exercise; exercised to complete exhaustion.
Oct. 6	1.55 P.M.	0.111	64	Blood before exercise.
	2.00	0.154	79	After 5 min. of exercise.
	2.10	0.256	79	After 15 min. of exercise.
	2.25	0.216	68	After ½ hr. of exercise.
	2.55	0.108	60	After ½ hr. of rest.
	4.10	0.107	50	After 1¼ hrs. of rest.

TABLE III.—DOG C3–49. NORMAL WEIGHT 16.9 KGM. COMPARISON ON NORMAL FASTING DOG OF EXERCISE, EXERCISE PLUS INTRAVENOUS GLUCOSE INJECTIONS, AND INTRAVENOUS GLUCOSE INJECTIONS ALONE.

Time.	Plasma sugar, per cent.			Hemoglobin, per cent.			Urine volume, c.c.			Urine glucose, per cent.			Rectal temperature, °F.*			Remarks.
	I.	II.	III.	I.	II.	III.	I.	II.	III.	I.	II.	III.	I.	II.	III.	
Before injection . .	0.133	0.106	0.119	111	99	94	..	..	..	0	0	0	102.1	102.7	102.7	Exercise started.
¼ hr. after 1st injection	0.154	0.166	0.167	120	94	80	..	20	10	..	1.00	1.54	103.8	104.6	102.8	
¼ hr. after 2d injection	0.172	0.142	0.154	116	96	78	..	20	2	..	1.49	+++	104.7	105.6	103.4	
¼ hr. after 3d injection	0.125	0.122	0.134	110	98	76	15	25	55	0	++	0.15	..	..	..	Exercise stopped.
½ hr. after 3d injection	..	0.100	..	..	95	..	..	10	..	..	0	..	104.9	104.2	103.4	
¾ hr. after 3d injection	..	0.133	..	..	95	..	..	25	..	..	0	..	..	104.7		
1 hr. after 3d injection	..	0.095	..	..	..	..	..	15	..	..	0	..	102.0	103.0	102.3	

I, exercise on fasting dog; II, exercise with intravenous glucose injections 1 gm. per kgm. per hr.; III, intravenous glucose injections 1 gm. per kgm. per hr. without exercise.

* High initial temperature due to hot weather.

TABLE IV.—DOG C3–54. NORMAL. WEIGHT, 19 KGM. COMPARISON OF EXERCISE, EXERCISE WITH INTRAVENOUS GLUCOSE INJECTIONS, AND INTRAVENOUS GLUCOSE INJECTIONS ALONE.

Time.	Plasma sugar, per cent.			CO_2, volume per cent.			Hemoglobin, per cent.			Urine volume, c.c.			Urine glucose, per cent.			Rectal temperature, °F.			Remarks.
	I.	II.	III.	I.	II.	III.	I.	II.	III.	I.	II.	III.	I.	II.	III.	I.	II.	III.	
Before injection	0.128	0.111	0.115	..	..	..	120	112	114	..	..	..	0	0	0	101.5	101.3	101.9	Exercise started.
15 min. after 1st injection	0.143	0.170	0.176	..	..	40.4	115	110	82	..	30	40	..	1.22	0.63	103.0	102.8	101.8	
15 min. after 2d injection	0.120	0.100	0.222	..	..	48.1	112	109	87	..	35	80	..	0.68	0.63	103.1	102.7	101.8	
15 min. after 3d injection	0.103	0.090	0.167	..	..	46.6	108	110	76	..	60	110	..	..	..	103.6	102.8	102.0	
15 min. after 4th injection	..	0.094	0.111	..	..	44.7	..	112	81	..	109	150	..	0	?	103.2	102.7	101.8	
½ hr. after 4th injection	..	0.094	..	..	..	..	..	1 12	..	..	39	..	..	0	..	102.1	102.5		
¾ hr. after 4th injection	..	0.098	..	..	..	..	..	..	..	..	65	..	..	0	..	..	102.6		
15 min. after 5th injection	..	..	0.128	..	..	46.2	..	..	81	..	..	125	..	..	0	..	..	101.8	
½ hr. after 5th injection	..	..	0.105	..	..	46.2	..	..	81	..	..	63	..	..	0	..	..	101.9	
¾ hr. after 5th injection	..	..	0.121	..	..	44.7	..	..	99	..	..	54	..	..	0	101.4	101.6	101.9	

I, exercise on fasting dog; II, exercise with intravenous glucose injections 1 gm. per kgm. per hr.; III, intravenous glucose injections 1 gm. per kgm. per hr. without exercise.

TABLE V.—DOG B2-00. PARTIALLY DEPANCREATIZED, NON-DIABETIC. WEIGHT 14 KGM. COMPARISON ON PARTIALLY DEPANCREATIZED DOG OF EXERCISE, EXERCISE WITH INTRAVENOUS GLUCOSE INJECTIONS, AND INTRAVENOUS GLUCOSE INJECTIONS ALONE.

Time.	Plasma sugar, per cent.			Hemoglobin, per cent.			Urine volume, c.c.			Urine glucose, per cent.			Rectal temperature, °F.			Remarks.
	I.	II.	III.	I.	II.	III.	I.	II.	III.	I.	II.	III.	I.	II.	III.	
1 hr. before injection	0.105	..	..	108												
Immediately before	0.125	0.108	0.105	102	104	112	28	..	..	0	0	0	101.5	101.5	101.3	Exercise started.
¼ hr. after 1st injection	0.125	0.125	..	98	97	..	..	25	..	..	0.54	..	103.4	103.2		
¼ hr. after 2d injection	0.133	0.161	0.288	95	95	98	..	19	90	..	0.56	0.95	104.2	103.8	101.0	
¼ hr. after 3d injection	..	0.113	0.145	..	102	91	..	70	100	..	..	0.50	103.7	102.8	101.6	
¼ hr. after 4th injection	0.105	0.089	0.091	98	95	93	6	120	175	0	..	0	103.1	102.7	102.2	Exercise stopped.
½ hr. after 4th injection	..	0.095	0.088	..	92	85	..	30	25	..	0	0	102.0	102.3	102.2	
¾ hr. after 4th injection	..	0.130	0.098	..	92	80	..	25	30	..	0	0	101.7	102.8	102.0	
After resting 2 hrs.	0.112	..	..	95	..	..	160	..	..	0	0	0				

I, exercise on fasting dog; II, exercise with intravenous glucose injections 1 gm. per kgm. per hr.; III, intravenous glucose injections 1 gm. per kgm. per hr. without exercise.

TABLE VI.—DOG B2-O1. NON-DIABETIC. WEIGHT 14 KGM. COMPARISON ON PARTIALLY DEPANCREATIZED DOG OF EXERCISE, EXERCISE WITH INTRAVENOUS GLUCOSE INJECTIONS, AND INTRAVENOUS GLUCOSE INJECTIONS ALONE.

Time.	Plasma sugar, per cent.			Hemoglobin, per cent.			Urine volume, c.c.			Urine glucose, per cent.			Rectal temperature, °F.			Remarks.
	I.	II.	III.	I.	II.	III.	I.	II.	III.	I.	II.	III.	I.	II.	III.	
1 hr. before injection	0.120	..	..	108												
Immediately before	0.125	0.099	0.111	108	101	108	15	..	..	0	0	0	101.4	101.2	101.3	Exercise started.
¼ hr. after 1st injection	0.125	0.102	0.167	..	97	108	..	30	44	..	0.93	0.54	102.8	103.0	102.0	
¼ hr. after 2d injection	0.133	0.127	0.176	107	97	90	..	20	55	..	0.84	0.89	103.2	102.6	102.2	
¼ hr. after 3d injection	..	0.118	0.173	..	94	87	..	45	90	..	0.25	0.43	104.0	103.6	102.4	
¼ hr. after 4th injection	0.150	0.094	0.154	106	90	80	10	60	100	0	0.34	+	103.8	103.0	102.3	Exercise stopped.
½ hr. after 4th injection	..	0.104	0.127	..	91	82	..	20	25	..	0	0	102.2	103.4	102.4	
¾ hr. after 4th injection	..	0.115	0.110	..	85	89	..	10	30	0	0	0	101.9	103.7	102.6	

I, exercise on fasting dog; II, exercise with intravenous glucose injections 1 gm. per kgm. per hr.; III, intravenous glucose injections 1 gm. per kgm. per hr.

TABLE VII.—DOG B2–O2. NON–DIABETIC. WEIGHT 10.5 KGM. COMPARISON ON PARTIALLY DEPANCREATIZED DOG OF EXERCISE, EXERCISE WITH INTRAVENOUS GLUCOSE INJECTIONS, AND INTRAVENOUS GLUCOSE INJECTIONS ALONE.

Time.	Plasma sugar, per cent.			Hemoglobin, per cent.			Urine volume, c.c.			Urine glucose, per cent.			Rectal temperature, °F.			Remarks.
	I.	II.	III.	I.	II.	III.	I.	II.	III.	I.	II.	III.	I.	II.	III.	
1 hr. before injection	0.114	..	..	119												
Immediately before	0.115	0.105	0.111	119	120	115	3	..	..	0	0	0	101.6	102.0	101.8	Exercise started.
¼ hr. after 1st injection	0.100	0.170	0.209	114	120	108	..	10	10	..	1.61	2.32	102.7	103.6	102.0	
¼ hr. after 2d injection	0.111	0.118	0.271	101	116	106	..	8	25	..	0.60	2.13	103.8	104.2	101.7	
¼ hr. after 3d injection	..	0.105	0.250	..	108	97	..	45	35	..	0.25	0.64	103.5	103.8	101.6	
¼ hr. after 4th injection	0.108	0.101	0.200	101	105	104	4	50	12	0	0.35	..	103.6	104.0	101.6	Exercise stopped.
½ hr. after 4th injection	..	0.104	0.137	..	100	103	..	15	10	..	0	0	102.7	104.0	101.4	
¾ hr. after 4th injection	..	0.128	0.125	..	96	99	..	10	10	..	0	0	101.5	103.8	101.7	

I, exercise on fasting dog; II, exercise with intravenous glucose injections 1 gm. per kgm. per hr.; III, intravenous glucose injections, 1 gm. per kgm. per hr. without exercise.

TABLE VIII.—DOG B2-71. WEIGHT, 16.8 KGM. MILD DIABETES.

Regular diet 1 kgm. lung, fed evenings. Improvement of assimilation of carbohydrate test-meal by exercise.

Date, 1915.	Hour.	Plasma sugar, per cent.	Hb., per cent.	Corp. vol., per cent.	Remarks.
July 19	12.00 M.	0.099	81	28.7	Blood before exercise; fed 100 gm. bread.
	12.45 P.M.	0.100	106	45.0	After ¾ hr. of hard exercise.
	2.45	0.218	99	34.3	After resting 2 hrs.
	5.00	0.118	116	....	Ran hard most of afternoon; almost collapsed at close; no glycosuria.
July 21	12.30 P.M.	0.112	90	27.2	Before feeding 100 gm. bread. At rest.
	3.15	0.286	82	....	2¾ hr. after feeding.
	5.30	0.286	..	32.5	5 hrs. after feeing; glycosuria 3.8 gm.
July 22	11.30 A.M.	0.124	82	32.2	Before exercise; exercised for 1 hr.; fed 100 gm. bread and exercise continued for ½ hr., rested for 1½ hrs.
	3.15 P.M.	0.109	89	36.5	After ¾ hr. of exercise.
	5.30	0.118	90	33.0	After 3 hrs. of exercise; no glycosuria.
July 23	12.15 P.M.	0.104	..	33.7	Blood before feeding 100 gm. bread; at rest.
	3.15	0.286	..	25.9	3 hrs. after feeding.
	5.45	0.149	..	36.0	5½ hrs. after feeding; glycosuria 4.5 gm.
July 26	12.30 P.M.	0.118	82	32.1	Before feeding 50 gm. glucose; at rest.
	2.15	0.400	86	28.3	1¾ hrs. after feeding.
	4.00	0.189	93	32.1	3½ hrs. after feeding.
	5.30	0.102	80	31.8	5 hrs. after feeding; glycosuria 3.6 gm.
July 27	12.30 P.M.	0.114	94	38.4	After 1 hr. of exercise; fed 50 gm. glucose.
	2.15	0.250	80	37.6	Exercised until 1.15; at rest until 1.50; exercised until 2.15.
	4.00	0.182	93	32.0	Ran hard all afternoon.
	5.30	0.143	104	36.0	Completely exhausted; glycosuria 0.3 gm.

TABLE IX.—DOG C3-66. WEIGHT, 20 KGM. SEVERE DIABETES. THE EFFECT OF EXERCISE ON FASTING DIABETIC DOG.

Time.	Plasma sugar, per cent.	Hb., per cent.	CO_2 vol. per cent.	Urine.		D:N ratio.
				Vol., c.c.	Glucose, per cent.	
Immediately before exercise	0.358	90	46.2	..	1.49	0.71
After ½ hr. exercise . .	0.370	90	38.5			
After 1 hr. exercise . .	0.455	84	34.7	2	Slight	..
After resting 1 hr. . .	0.435	73	46.2	34	3.13	4.05

TABLE X.—DOG B2–89. WEIGHT, 13.2 KGM. SEVERE DIABETES. COMPARISON ON PARTIALLY DEPANCREATIZED DOG, SEVERELY DIABETIC, OF EXERCISE WITH INTRAVENOUS GLUCOSE INJECTIONS AND INTRAVENOUS GLUCOSE INJECTIONS ALONE.

Time.	Plasma sugar, per cent.		Hemoglobin, per cent.		Urine volume, c.c.		Urine sugar, per cent.		Rectal temperature, °F.		Remarks.
	I.	II.	I.	II.	I.	II.	I.	II.	I.	II.	
Before injection . . .	0.133	0.122	117	112	..	..	0	0	101.8	101.2	Exercise started.
¼ hr. after 1st injection .	0.264	0.256	109	111	25	16	2.22	4.00	104.0	103.8	
¼ hr. after 2d injection .	0.400	0.333	93	100	52	30	3.30	5.00	104.0	104.9	
½ hr. after 2d injection .	0.264	0.278	100	74	10	9	3.30	3.83	105.5	104.5	
¾ hr. after 2d injection .	0.218	0.250	105	76	5	4	++	0.40	105.0	103.9	
1 hr. after 2d injection .	0.103	0.141	98	83	5	2	+	++	104.4	103.4	Exercise stopped.
1½ hr. after 2d injection .	0.131	0.122	86	78	6	4	0	+++	102.5	104.2	

I, exercise with intravenous glucose injections, 1 gm. per kgm. per hr.; II, intravenous glucose injections, 1 gm. per kgm. per hr. without exercise.

TABLE XI.—DOG B2–79. WEIGHT 15 KGM. INCREASINGLY SEVERE DIABETES.

Date.	Hour.	Plasma sugar, per cent.	Hb., per cent.	Corp. vol., per cent.	CO_2, vol. per cent.	Urine sugar, per cent.	Remarks.
1915.							
July 17	10.30 A.M.	0.133	100	46.2	..	..	Blood taken before exercise.
	12.30 P.M.	0.100	120	49.0	..	..	After exercising hard for 2 hrs.
July 23	2.30 P.M.	0.109	105	45.3	..	..	Before exercise.
	6.00	0.105	125	49.5	..	..	After 3½ hrs. hard exercise.
Sept. 25	12.15 P.M.	0.169	110	50.0	..	..	After 5 min. of exercise.
	1.10	0.143	110	52.0	..	..	After 1 hr. of exercise.
Dec. 1	10.40 A.M.	0.278	111	43.5	..	1.03	Before exercise; fasting.
	1.40 P.M.	0.278	104	40.0	..	0.25	Immediately before exercise.
	1.50	0.313	108	48.5	..	..	After 10 min. of exercise.
	2.05	0.159	98	..	..	..	After 25 min. of exercise.
	2.40	0.143	97	..	..	..	After 1 hr. of exercise.
	3.40	0.256	97	41.0	..	Faint	After 2 hrs. of exercise.
Dec. 6	1.50 P.M.	0.200	..	..	..	0	Before exercise fed 500 gm. lung; allowed to rest ½ hr. before exercise.
	4.50 P.M.	0.208	..	..	..	Slight	After 2½ hrs. of exercise.
1916.							
Feb. 3	1.50 P.M.	0.278	95	..	..	Very faint	1 hr. before exercise; fasting.
	2.50	0.334	95	..	..	Very faint	Immediately before exercise.
	3.05	0.264	98	..	..	..	After 15 min. of exercise.
	3.20	0.304	103	..	..	..	After ½ hr. of exercise.
	3.50	0.278	105	..	..	Slight	After 1 hr. of exercise.
	4.50	0.294	..	..	..	0	After resting 1 hr.
Mar. 30	3.20 P.M.	0.455	90	..	42.3	0.61	Before exercise; fasting; D:N ratio 1.90.
	3.50	0.312	82	..	31.9	..	After ½ hr. of exercise.
	4.20	0.435	72	..	34.7	0.97	After 1 hr. of exercise; D:N ratio 6.45.
	5.20	0.435	72	..	42.3	0.78	After resting 1 hr.; D:N ratio 2.30.

Dog B2–79. (Tables XI and XII and Chart III.)

Dog B2–79, as described in the preceding paper, was fattened so as to produce steady aggravation of the diabetes, while the successive recurrences of glycosuria were checked by reduction of protein and substitution of fat. Table XI illustrates the effects of exercise in the different stages of progress on days without feeding. On July 17 and 23 the plasma sugar was low and was reduced a trifle by exercise. On September 25 hyperglycemia was present but was lowered by exercise. On December 1 the hyperglycemia was greater; it rose sharply with ten minutes of exercise, then fell during the first hour, but showed a rising tendency at the end of the second hour. On December 6 exercise seemed to prevent the usual rise of blood sugar after protein feeding, but it is possible that digestion was delayed. On February 3 fluctuations of the hyperglycemia occurred, but any effect of exercise is doubtful.

TABLE X.—DOG B2–89. WEIGHT, 13.2 KGM. SEVERE DIABETES. COMPARISON ON PARTIALLY DEPANCREATIZED DOG, SEVERELY DIABETIC, OF EXERCISE WITH INTRAVENOUS GLUCOSE INJECTIONS AND INTRAVENOUS GLUCOSE INJECTIONS ALONE.

Time.	Plasma sugar, per cent.		Hemoglobin, per cent.		Urine volume, c.c.		Urine sugar, per cent.		Rectal temperature, °F.		Remarks.
	I.	II.	I.	II.	I.	II.	I.	II.	I.	II.	
Before injection . . .	0.133	0.122	117	112	..	..	0	0	101.8	101.2	Exercise started.
¼ hr. after 1st injection .	0.264	0.256	109	111	25	16	2.22	4.00	104.0	103.8	
¼ hr. after 2d injection .	0.400	0.333	93	100	52	30	3.30	5.00	104.0	104.9	
½ hr. after 2d injection .	0.264	0.278	100	74	10	9	3.30	3.83	105.5	104.5	
¾ hr. after 2d injection .	0.218	0.250	105	76	5	4	++	0.40	105.0	103.9	
1 hr. after 2d injection .	0.103	0.141	98	83	5	2	+	++	104.4	103.4	Exercise stopped.
1½ hr. after 2d injection .	0.131	0.122	86	78	6	4	0	+++	102.5	104.2	

I, exercise with intravenous glucose injections, 1 gm. per kgm. per hr.; II, intravenous glucose injections, 1 gm. per kgm. per hr. without exercise.

TABLE XI.—DOG B2–79. WEIGHT 15 KGM. INCREASINGLY SEVERE DIABETES.

Date.	Hour.	Plasma sugar, per cent.	Hb., per cent.	Corp. vol., per cent.	CO_2, vol. per cent.	Urine sugar, per cent.	Remarks.
1915.							
July 17	10.30 A.M.	0.133	100	46.2	..	..	Blood taken before exercise.
	12.30 P.M.	0.100	120	49.0	..	..	After exercising hard for 2 hrs.
July 23	2.30 P.M.	0.109	105	45.3	..	..	Before exercise.
	6.00	0.105	125	49.5	..	..	After 3½ hrs. hard exercise.
Sept. 25	12.15 P.M.	0.169	110	50.0	..	..	After 5 min. of exercise.
	1.10	0.143	110	52.0	..	..	After 1 hr. of exercise.
Dec. 1	10.40 A.M.	0.278	111	43.5	..	1.03	Before exercise; fasting.
	1.40 P.M.	0.278	104	40.0	..	0.25	Immediately before exercise.
	1.50	0.313	108	48.5	..	..	After 10 min. of exercise.
	2.05	0.159	98	..	..	..	After 25 min. of exercise.
	2.40	0.143	97	..	..	..	After 1 hr. of exercise.
	3.40	0.256	97	41.0	..	Faint	After 2 hrs. of exercise.
Dec. 6	1.50 P.M.	0.200	..	..	..	0	Before exercise fed 500 gm. lung; allowed to rest ½ hr. before exercise.
	4.50 P.M.	0.208	..	..	..	Slight	After 2½ hrs. of exercise.
1916.							
Feb. 3	1.50 P.M.	0.278	95	..	..	Very faint	1 hr. before exercise; fasting.
	2.50	0.334	95	..	..	Very faint	Immediately before exercise.
	3.05	0.264	98	..	..	..	After 15 min. of exercise.
	3.20	0.304	103	..	..	..	After ½ hr. of exercise.
	3.50	0.278	105	..	..	Slight	After 1 hr. of exercise.
	4.50	0.294	..	..	..	0	After resting 1 hr.
Mar. 30	3.20 P.M.	0.455	90	..	42.3	0.61	Before exercise; fasting; D:N ratio 1.90.
	3.50	0.312	82	..	31.9	..	After ½ hr. of exercise.
	4.20	0.435	72	..	34.7	0.97	After 1 hr. of exercise; D:N ratio 6.45.
	5.20	0.435	72	..	42.3	0.78	After resting 1 hr.; D:N ratio 2.30.

Dog B2–79. (Tables XI and XII and Chart III.)

Dog B2–79, as described in the preceding paper, was fattened so as to produce steady aggravation of the diabetes, while the successive recurrences of glycosuria were checked by reduction of protein and substitution of fat. Table XI illustrates the effects of exercise in the different stages of progress on days without feeding. On July 17 and 23 the plasma sugar was low and was reduced a trifle by exercise. On September 25 hyperglycemia was present but was lowered by exercise. On December 1 the hyperglycemia was greater; it rose sharply with ten minutes of exercise, then fell during the first hour, but showed a rising tendency at the end of the second hour. On December 6 exercise seemed to prevent the usual rise of blood sugar after protein feeding, but it is possible that digestion was delayed. On February 3 fluctuations of the hyperglycemia occurred, but any effect of exercise is doubtful.

TABLE XII.—DOG B2-79.

Time.	Nov. 8.			Nov. 11.			Nov. 12.			Nov. 26. Plasma sugar, per cent.	Nov. 29. Plasma sugar, per cent.
	Plasma sugar, per cent.	Hb., per cent.	Corp. vol., per cent.	Plasma sugar, per cent.	Hb., per cent.	Corp. vol., per cent.	Plasma sugar, per cent.	Hb., per cent.	Corp. vol., per cent.		
Before exercise or food	0.125	116	53.0	0.161	115	57.8	0.115	109	40.0	0.156	0.154
¾ hr. after food	0.142	110	50.0	0.133	115	50.0	0.115	105	41.0		
1 hr. after food	0.184	112	51.0	0.142	113	44.0					
1¾ hr. after food	0.167	114	..	0.130	109	51.0	0.108	105	44.5		
3 hr. after food	0.128	112	58.0	0.139	100	47.5	0.111	..	..	0.182	
4 hr. after food	0.147	114	51.0	..	..	..	..	..	..	..	
5 hr. after food	0.141	109	65.0	..	..	..	..	..	..	0.250	0.208

A, fed 500 gm. lung; Nov. 8, at rest; Nov. 11 and 12, with exercise. B, fed 1 kgm. lung; Nov. 26, at rest; Nov. 29, with exercise.

On March 30 there was a fall of plasma sugar, particularly after thirty minutes of exercise, but the actual effect was injury rather than benefit, as shown in the extra sweeping out of sugar represented in the D:N ratios.

Table XII shows protein-feeding experiments on the same dog during November, 1915. A real improvement of assimilation with exercise at this stage, as opposed to a mere slowing of food absorption, is indicated by the fact that the plasma sugar elevations were longer as well as higher on rest days, and also on a second exercise day (November 12) were lower than on the day before. There was no glycosuria.

Dog B2–80. (Table XIII and Chart V.)

Dog B2–80, as described in the preceding paper, progressed to severe diabetes and acidosis on excessive feeding, particularly with fat. Toward the end exercise was tried on several days. The dog was strong and willing and ran hard. The plasma sugar was increased rather than diminished. The rectal temperature rose as usual above 104° F. during exercise. Acidosis was present throughout, as indicated by nitroprusside reactions in blood and urine and rather low plasma bicarbonate values, but the former did not increase and for some reason the bicarbonate concentration actually rose with the running. There were also no coma symptoms even when the dog ran to exhaustion. This was the more remarkable because coma was so near. No exercise was used after August 8 and the condition appeared unchanged. Vomiting began on August 11, and coma on August 13.

TABLE XIII.—DOG B2–80. WEIGHT, 17 KGM.

Date.	Hour.	Plasma sugar, per cent.	Hb., per cent.	Corp. vol., per cent.	Urine.		Remarks.
					Vol., c.c.	Sugar, per cent.	
July 23	2.30 P.M.	0.263	114	49.0	..	..	Before exercise; fasting.
	6.15	0.270	120	55.5	..	..	After 3¾ hrs. of hard exercise
July 26	11.30 A.M.	0.208	118	50.3	..	..	Before exercise.
	12.30 P.M.	0.208	125	53.6	..	..	After 1 hr. of exercise.
Aug. 8	10.50 A.M.	0.294	103	55.0	..	0.66	Before exercise.
	11.00	0.294	101	56.0	6	0.56	After 10 min. of hard exercise.
	12.20 P.M.	0.322	94	61.0	9	1.67	After resting 1 hr. 20 min.
	12.50	0.333	105	64.5	5	1.23	After ½ hr. of very hard exercise; exhausted.
	4.30	0.303	104	53.4	16	1.25	After resting 3 hrs. 40 min.

Dog C3–18. (Table XIV and Chart V.)

Dog C3–18 was a graft animal with diabetes, like dog C3–02. The period covered in Table XIV represents gain in tolerance, apparently due in part to exercise. There was a fixed diet of beef-lung and pancreas, on which the body weight declined by about three-fourths of a kilo during this period, so that part of the improve-

ment of assimilation may be attributed to undernutrition; but the exercise must also have contributed toward the undernutrition.

On November 15 exercise failed to prevent a great rise of blood sugar after feeding or stop the existing glycosuria. November 16 the initial blood sugar was higher but did not rise during one and a half hours. November 17 the urine was free from sugar. With continuous rest thereafter, except for a single exercise day on November 19, glycosuria remained absent through November 23. It was present on November 24, 25 and 26 and ceased with a single exercise day on November 26. The table shows a rise of blood sugar after feeding on the rest day November 27 and none on the exercise day November 26. Glycosuria remained absent. On November 29 exercise reduced the blood sugar. The dog was fed that evening, but not on November 30. On December 1 the blood sugar fell during two hours of exercise and rose during the ensuing one and a half hours of rest.

The record suggests not only that exercise facilitated assimilation, but also that it was more effective after the tolerance had been improved by undernutrition. (See also Chart V.)

TABLE XIV.—DOG C3–18. WEIGHT, 15 KGM.

Date.	Hour.	Plasma sugar, per cent.	Urine sugar, gm. in 24 hours.	Remarks.
1915.				
Nov. 15	10.35 A.M.	0.188	2.94	Blood taken before exercise; fed usual diet.
	11.30	0.256	....	After 20 min. of exercise; rather weak; cannot be exercised long at a time.
	2.50 P.M.	0.555	....	After resting 3½ hrs.
Nov. 16	9.45 A.M.	0.238	0	Before exercise; fasting.
	10.15	0.222	....	After ½ hr. of exercise; exercise stopped.
	10.35	0.222	....	After resting ½ hr.; exercise started.
	11.05	0.238	....	After ½ hr. of exercise; urine for the period 12 c.c.; negative sugar.
Nov. 26	2.00 P.M.	0.186	0	Before exercise; fed usual diet.
	4.30	0.182	....	After 2½ hrs. of exercise.
Nov. 27	1.00 P.M.	0.208	0	Before feeding; fed usual diet; at rest.
	3.30 P.M.	0.262	....	After resting 2½ hrs.
Nov. 29	1.55 P.M.	0.218	0	Before exercise.
	3.30	0.147	....	After 1½ hrs. of exercise.
Dec. 1	10.10 A.M.	0.196	0	Fasting for 36 hrs.; blood taken before exercise.
	12.10 P.M.	0.162	....	After two hrs. of exercise.
	1.45	0.196	....	After resting 1½ hrs.; urine for the period 95 c.c.; negative sugar.

Dog C3–22. (Table XVI and Chart V.)

Dog C3–22. Severe diabetes, controlled four months by diet, first 1 kilo of lung, then 400 gm. lung and 200 gm. suet, then 300 gm. lung and 200 gm. suet, then 200 gm. lung and 200 gm. suet. The recurrences of glycosuria were checked each time by the reduction of protein, but the usual gradual aggravation occurred on the high calory diets, and at the time of these experiments glycosuria

TABLE XV.—DOG C3-19. SEVERE DIABETES.

Date.	Hour.	Plasma sugar, per cent.	Hb., per cent.	Corp. vol., per cent.	Urine sugar, per cent.	Remarks.
Aug. 11	3.00 P.M.	0.250	87	36.7	0	Before feeding 500 gm. lung; at rest.
	6.00	0.276	80	35.2	3.84	3 hrs. after feeding.
	11.30	0.303	90	34.6	6.66	8½ hrs. after feeding; glucose excreted 6.4 gm.
Aug. 12	12.00 M.	0.294	85	35.0	2.22	Before exercise; fed 500 gm. lung.
	12.40 P.M.	0.345	..	..	..	Exercised from 12.15 to 12.40; glucose excreted before exercise 3.5 gm.
	1.00	0.286	98	40.0	2.27	Exercised from 12.45 to 1; glucose excreted after exercise 2.3 gm.
	3.00	0.263	88	31.5	1.58	After alternate rest and exercise periods.
	8.45	0.192	84	30.2	0.75	Exercised until 6.30, rest thereafter.

Dog C3–19, weighing 11.1 kilos, tolerated 500 gm. lung on August 9 without glycosuria, but showed glycosuria of 1.1 gm. on August 10. On the two following days rest and exercise were compared with results shown in Table XV. The increasing glycosuria was arrested by exercise, inasmuch as 3.5 gm. glucose was excreted during the forenoon of August 12 without exercise or food, and only 2.3 gm. during the remainder of the twenty-four hours with feeding and exercise.

TABLE XVI.—DOG C3-22. NORMAL WEIGHT, 13.4 KGM. SEVERE DIABETES.

Date.	Hour.	Plasma sugar, per cent.	Urine sugar, gm. in 24 hours.	Remarks.
1915.				
Nov. 12	10.15 A.M.	0.222	Faint	Before exercise; fed usual diet.
	11.20	0.238	....	After 1 hr. of exercise.
	3.00 P.M.	0.322	3.1	After 3½ hrs. of rest.
Nov. 13	2.00 P.M.	0.145	1.6	Before exercise; fasting.
	3.00	0.125	....	After 1 hr. of exercise.
	4.00	0.125	....	After 2 hrs. of exercise.
Nov. 14	....	....	Slight	Rest day.
Nov. 15	10.25 A.M.	0.200	1.7	Before exercise; fed usual diet.
	12.00 M.	0.250	....	After 1 hr. of exercise.
	1.30 P.M.	0.263	....	After resting 1½ hrs.
	2.30	0.182	....	After 1 hr. of exercise.
	3.00	0.170	....	After 1½ hrs. of exercise.
	4.20	0.257	....	After resting 1 hr. 20 min.
Nov. 16	9.35 A.M.	0.159	Faint	Before exercise; fasting.
	10.35	0.154	....	After 1 hr. of exercise.
	11.35	0.154	....	After 2 hr. of exercise.
Nov. 26	2.05 P.M.	0.227	Faint	Before exercise; fed usual diet.
	4.30	0.186	....	After 2¼ hrs. of exercise.
Nov. 27	10.50 A.M.	0.256	1.3	Fed usual diet; no exercise.
	2.50 P.M.	0.400	....	4 hrs. after feeding.
Nov. 28	....	....	1.1	Exercise day.
Nov. 29	1.55 P.M.	0.227	0.3	Before exercise; fasting.
	3.30	0.170	....	After 1½ hrs. of exercise.
Nov. 30	....	....	....	Fast day.
Dec. 1	10.10 A.M.	0.200	0	Before exercise; fasting.
	12.10 P.M.	0.128	....	After 2 hrs. of exercise.
	1.45	0.200	....	After resting 1 hr. 35 min.
Dec. 6	1.50 P.M.	0.313	1.2	Before exercise; fed usual diet; rested ½ hr. before beginning exercise.
	4.50	0.500	....	After 2¼ hrs. of exercise.
Dec. 7	....	....	2.7	Rest day.
Dec. 8	....	....	3.5	Rest day.
Dec. 9	....	....	13.6	Rest day.

was returning on the diet last mentioned. Exercise was begun November 12 in the attempt to stop the downward progress. The weight was then 11.5 kgm.

November 12, hyperglycemia increased after feeding notwithstanding exercise, but by the next day there was reduction of hyperglycemia and glycosuria. Both were found higher on November 15, after the preceding rest day, but an alternation of rest and exercise (November 15) showed that exercise reduced the blood sugar. On November 16 the fasting blood sugar was lower but was not appreciably reduced by exercise. Hard exercise was then given every day, both before and after feeding, through November 19; no blood sugar analyses were made, but glycosuria remained absent.

Beginning November 20 the dog remained at rest. Traces of glycosuria began November 25 and increased the next day. On that day (November 26) exercise was given; the blood sugar was lowered and the glycosuria remained too small to titrate. November 27 was a control day without exercise and showed a marked rise of blood and urine sugars as compared with November 26.

Exercise was then continued and reduced the glycosuria but failed to abolish it until the fast day of November 30. The regular diet of 200 gm. lung and 200 gm. suet then continued, with the hardest possible exercise occupying the greater part of every day. Nevertheless, traces of glycosuria began December 2 and gradually increased to 1.2 gm. on December 6. Exercise thus finally failed to suppress hyperglycemia and glycosuria, but evidently restrained them somewhat, as shown by the rapid increase with discontinuance of exercise following December 6.

Dog C3–02. (Table XVII.)

Dog C3–02 was an animal with moderate diabetes, having no pancreas tissue except a subcutaneous graft, of which the pedicle had been cut so as to isolate it from all intra-abdominal connections. Table XVII shows that exercise had the usual effect in restraining the rise of blood sugar after feeding, and thus excludes any nervous influence upon the pancreas as the cause of this action.

TABLE XVII.—DOG C3–02. SUBCUTANEOUS GRAFT.

Date.	Hour.	Plasma sugar, per cent.	Hb., per cent.	Rectal temp., ° F.	Remarks.
1915.					
Aug. 10	11.30 A.M.	0.120	95		Blood taken; dog allowed to rest quietly in cage.
	3.30 P.M.	0.145	91	..	Blood taken after resting 4 hrs.; fed 600 gm. lung, 600 gm. raw pancreas and 100 gm. suet.
	6.00	0.286	100	..	Blood taken 2½ hrs. after eating.
Aug. 11	12.25 P.M.	0.139	88	102.4	Blood taken before exercise.
	1.00	0.154	97	103.5	After ½ hr. of exercise.
	3.30	0.164	98	..	After 2½ hrs. of rest; fed same diet as on Aug. 10.
	4.30	0.151	..	104.8	After 1 hr. of exercise.
	6.00	0.164	..	105.5	After 2½ hrs. of exercise.

TABLE XVIII.—THE EFFECT OF EXERCISE ON TOTALLY DEPANCREATIZED DOGS.

DOG C3-60.

Time.	Blood.						Urine.				D:N ratio.	
	Plasma sugar, per cent.		CO_2, volume per cent.		Nitroprussiade reaction.		Volume, c.c.		Sugar, per cent.			
	Feb. 24.	Feb. 25.	Feb. 24.	Feb. 25.	Feb. 24.	Feb. 25.	Feb. 24.	Feb. 25.	Feb. 24.	Feb. 25.	Feb. 24.	Feb. 25.
Before exercise	0.264	0.270	40.0	46.2	..	Faint	..	..	4.76	3.70	2.22	1.54
After ¼ hr. exercise	0.294	0.333	39.0	38.5	..	Faint	0	..	..	..		
After ½ hr. exercise	0.346	0.358	38.1	33.8	..	Faint	5	13	3.40	0.95	..	3.28

DOGS C3-65 AND C3-76.

Time.	Blood.								Urine.					
	Plasma sugar, per cent.		Hemoglobin, per cent.		CO_2, volume per cent.		Total acetone, mgm. per 100 c.c.		Volume, c.c.		Sugar, per cent.		D:N ratio.	
	Dog C3-65.	Dog C3-76.	Dog C3-65.	Dog C3-76.	Dog C3-65.	Dog C3-76.	Dog C3-65.	Dog C3-76.	Dog C3-65.	Dog C3-76.	Dog C3-65.	Dog C3-76.	Dog C3-65.	Dog C3-76.
Before exercise	0.385	0.500	94	95	51.0	44.3	Mod.	33.1	..	..	3.12	2.21	1.75	2.50
After ½ hr. exercise	0.455	..	89	..	44.3	..	Slight							
After 1 hr. exercise	..	0.500	..	84	..	38.5	..	48.3	4	5	2.38	2.67	1.88	3.45
After 1 hr. rest	..	0.500	..	89	..	44.3	..	26.6	0	32	..	4.00		

TABLE XIX.—DOG C3–53. WEIGHT 12.3 KGM. THE EFFECT OF EXERCISE ON A PHLORIZINIZED DOG.

Time.	Dec. 27, before giving phlorizin.				Dec. 28, phlorizin and exercise.				Dec. 29, phlorizin and exercise.				Dec. 30, phlorizin without exercise.			
	Plasma sugar, per cent.	Hb., per cent.	Urine.		Plasma sugar, per cent.	Hb., per cent.	Urine.		Plasma sugar, per cent.	Hb., per cent.	Urine.		Plasma sugar, per cent.	Hb., per cent.	Urine.	
			Vol., c.c.	Sugar, per cent.			Vol., c.c.	Sugar, per cent.			Vol., c.c.	Sugar, per cent.			Vol., c.c.	Sugar, per cent.
1 hr. before exercise	0.111	112	45	0	0.097	106	28	7.15	0.077	101	290	7.82	0.095	86	124	6.60
Immediately before exercise	..	..	..	..	0.112	106	25	7.70	0.092	110	25	8.25	0.083	86	14	6.72
After 15 min. of exercise	..	..	..	..	0.159	110	..	..	0.082	104						
After ½ hr. of exercise	..	..	..	..	0.119	108	..	..	0.119	100						
After 1 hr. of exercise	..	..	..	..	0.125	95	20	9.10	0.132	108	25	10.0				
After resting 2 hrs.	..	..	..	..	0 118	92	55	7.70	0.100	95	175	2.5	0.081*	..	67*	6.62*
After resting 5 hrs.	..	..	..	..	0.108	106	50	7.70	0.072	..	75	5.5				

* Taken 2½ hours after previous blood, dog at rest all the time.

TABLE XX.—COMPARISON ON A PHLORIZINIZED DOG OF INTRAVENOUS SUGAR INJECTIONS, INTRAVENOUS SUGAR INJECTIONS WITH EXERCISE, AND EXERCISE ALONE.

	Intravenous sugar injections.					Intravenous sugar injections with exercise.					Exercise without injections.					
	Plasma sugar, per cent.	Hb., per cent.	Urine.		D:N.	Plasma sugar, per cent.	Hb., per cent.	Urine.		D:N.	Plasma sugar, per cent.	Hb., per cent.	Urine.		D:N.	Remarks.
			Vol., c.c.	Sugar, per cent.				Vol., c.c.	Sugar, per cent.				Vol., c.c.	Sugar, per cent.		
Before injection or exercise	0.095	95	65	1.32	4.02	0.056	112	33	5.40		0.080	95	54	3.70	3.80	Exercise started
15 min. after 1st injection	0.178	80	110	3.03	..	0.181	..	14	6.25							
15 min. after 2d injection	0.193	80	106	3.12	..	0.161	90	24	4.00		0.095	108	..	..	..	After ½ hr. exercise.
15 min. after 3d injection	0.214	80	130	1.88	..	0.250	98	19	2.50							
	..	..	..	..	..	..	..	..	..		0.087	105	..	3.57	4.26	After 1 hr. exercise.
½ hr. after 3d injection	0.193	77	81	1.53	..	0.118	92	8	2.78							
45 min. after 3d injection	0.143	77	62	1.51	..											

TABLE XXI.—DOG C3-57. WEIGHT 14 KGM. PHLORIZINIZED.

Time.	Blood.				Urine.				Remarks.
	Plasma sugar, per cent.	Hb., per cent.	CO_2, vol. per cent.	Nitro-prusside reaction.	Volume, c.c.	Sugar, per cent.	D:N ratio.	Nitro-prusside reaction.	
Mar. 2.									
8.00 A.M. . .	0.065	92	41.4	Faint	..	3.03	3.24	Very heavy	
11.00 A.M. . .	0.080	95	41.4	Faint	54	3.70	3.80	Very heavy	Started exercise.
11.30 A.M. . .	0.095	108	33.8	Faint					
12.00 M. . .	0.087	105	36.6	Slight	6	3.57	4.26	Heavy	Exercise finished; some urine lost on treadmill.
Mar. 3.									
10.40 A.M. . .	0.056	112	40.4	Slight	..	5.90	..	Mod.	10.50 finished 1st intravenous glucose 0.5 gm. per kgm. and exercise started.
11.05 A.M. . .	0.182	..	39.5	0	14	6.25	..	Faint	11.20 finished 2d injection.
11.40 A.M. . .	0.161	90	33.8	0	24	4.00	..	0	11.58 finished 3d injection.
12.15 P.M. . .	0.250	98	36.6	0	19	2.50	..	0	
12.30 P.M. . .	0.118	92	38.5	0	8	2.78	..	0	Urine lost on treadmill; exercise stopped.

Note on Tables XIX, XX and XXI.

These fasting dogs received 1 gm. phlorizin in oil suspension subcutaneously daily. Mobilization of extra sugar is indicated by the rise of blood sugar and also of the D:N ratios, according to the principles made familiar by Lusk. It may further be noted (Dog C3-57) that the absolute sugar excretion was diminished, at least for the brief experimental period, by reduction of the volume of urine by exercise. It was not determined whether the intravenously injected glucose was quantitatively excreted, but the nitroprusside reactions in blood plasma and urine were cleared up.

THERAPEUTIC RESULTS OF LONG-CONTINUED EXERCISE.

Dog B2–86.

Dog B2–86 was described in Paper 2 of Series I[8] as an animal in which prolonged maximal feeding of starch and sugar barely failed to break down the tolerance. In this and a series of similar dogs the attempt was made to keep up the failing appetite with exercise, in the hope that the tolerance might finally break down, but the existing glycosuria merely cleared up more quickly and remained absent. Prolonged overfeeding with exercise therefore failed to produce diabetes in dogs which were non-diabetic on feeding alone.

Dog B2–43. (Table XXII.)

Dog B2–43 was an animal with mild diabetes, free from glycosuria on a diet of 1 kilo of lung, fed evenings, but with a limited tolerance for bread, as shown in the experiments in Paper 2 of Series I. In July, 1915, experiments were performed, indicating a better assimilation of carbohydrate test-meals on exercise days than on rest days, as shown in Table XXII. The weight during this time was stationary at 10.5 kilos.

After a few experiments with cold, as described in a later paper, the dog was left at rest, and a beneficial after-effect of the exercise was indicated by the continued absence of glycosuria on the diet of 1 kilo lung and 100 gm. bread. On this diet without exercise the weight rose to 12 kilos by August 31, when glycosuria began with 0.7 per cent. sugar in 450 c.c. urine, increasing to 1.4 per cent. in 419 c.c. urine on September 1. With exercise this glycosuria immediately dropped to faint traces and ceased September 2. Exercise was then continued to the extent of an hour or two daily after the carbohydrate feeding; glycosuria thus remained absent while the weight rose to 12.8 kilos by September 10.

With omission of exercise, September 10 to 17, there was daily glycosuria from 0.16 to 0.9 per cent., while the weight rose to 14 kilos.

Heavy exercise was then resumed and at the same time the bread increased to 150 gm. daily. The weight thus gradually fell to 11.8 kilos on October 6 and glycosuria was continuously absent. On October 6 the bread was increased to 250 gm., still without glycosuria, but the dog now left most of the lung uneaten, and the weight thus fell further to 10.6 kilos on October 20.

Exercise was then stopped and 100 gm. lard added to the diet. Glycosuria remained absent, even though the weight gradually rose to 14.5 kilos by the following March. With an unlimited diet of bread only, the glycosuria then returned.

The final marked improvement was doubtless due largely to recuperation in the pancreas remnant, but this was evidently favored by exercise. Though the earlier experiments indicated that exercise favored assimilation even when the weight rose, the benefit was doubtless greater when the weight was reduced. It may be inferred that reduction of weight is beneficial even when it is produced by the increased metabolism of exercise instead of by reduction of the food supply.

TABLE XXII.—DOG B2-43. MILD DIABETES.

Date.	Hour.	Plasma sugar, per cent.	Hb., per cent.	Corp. vol., per cent.	Remarks.
July 17	9.30 A.M.	0.111	98	43.7	Started exercise; fasting.
	11.00	0.106	99	39.3	After 1½ hrs. of exercise.
July 19	12.00 M.	0.118	104	43.0	Blood taken before feeding 100 gm. bread; 12.15 started exercise.
	12.45 P.M.	0.118	83	43.0	After ½ hr. of exercise.
	2.30	0.228	95	40.0	After resting 1¾ hrs.
	5.00	0.085	98	40.5	After 2½ hrs. of exercise.
July 21	12.30 P.M.	0.153	90	43.5	Before feeding 100 gm. bread; at rest.
	3.00	0.178	96	45.0	2½ hrs. after feeding.
	5.30	0.222	..	37.1	5 hrs. after feeding.
July 22	12.30 P.M.	0.125	97	38.0	After 1 hr. of exercise, fed 100 gm. bread; exercised until 1 P.M.
	3.15	0.115	94	38.5	Rested in cage until 2.30, then started exercise; blood taken after ¾ hr. of exercise.
	5.30	0.111	96	37.5	After 3 hrs. of exercise.
July 23	12.15 P.M.	0.125	96	37.3	Before feeding 100 gm. bread; at rest.
	3.15	0.217	93	37.0	3 hrs. after feeding.
	5.45	0.133	..	35.3	5½ hrs. after feeding.
July 24	12.00 M.	0.128	86	40.8	After 2 hrs. of exercise; fed 100 gm. of bread and by mistake 1 kgm. lung; rested remainder of day.
	3.15 P.M.	0.244	91	40.8	3¼ hrs. after feeding.
	5.30	0.270	81	38.0	5½ hrs. after feeding.
July 26	12.00 M.	0.115	83	35.0	Before feeding 50 gm. glucose.
	1.45 P.M.	0.294	92	36.5	1¾ hrs. after feeding.
	4.00	0.112	80	37.0	4 hrs. after feeding.
	5.30	0.137	88	36.0	5½ hrs. after feeding.
July 27	12.30 P.M.	0.156	95	37.0	After ¾ hrs. of exercise; 12.30 P.M. fed 50 gm. glucose.
	2.15	0.123	84	35.0	Exercise continued to 1.15, rested in cage to 2.15.
	4.30	0.107	70	45.0	
	6.00	0.100	73	37.8	Exercised from 2.15 to 6.00 P.M.

Dog B2-88. (Tables XXIII and XXIV and Chart IV.)

Dog B2-88 was mildly diabetic three months after operation, sugar-free on 1 kilo of beef-lung daily, but with glycosuria between 1 and 2 per cent. with 100 gm. bread. At this stage (July 12, 1915), at a weight of 12 kilos, 25 gm. bread was added to the diet

and exercise begun. With increasing exercise the bread was increased to 50 gm. on July 18 and to 100 gm. on July 27 without glycosuria.

TABLE XXIII.—DOG B2–88. MODERATE DIABETES.

Time.	Plasma sugar, per cent.					
	Nov. 9.	Nov. 10.	Nov. 11.	Nov. 12.	Nov. 18.	Nov. 27.
Before exercise or feeding	0.189	0.114	0.122	0.122	0.143	0.137
After ¼ hr. of exercise	....	....	....	0.135		
After ½ hr. of exercise	....	....	....	0.125		
After 1 hr. of exercise	....	....	....	0.112		
¼ hr. after eating	0.169	....	....	....	0.143	0.154
½ hr. after eating	0.250	....	....	....	0.147	0.173
¾ hr. after eating	....	....	0.149			
1 hr. after eating	0.257	0.133	0.167	0.145	0.166	0.257
1¼ hr. after eating	....	....	0.143			
2 hrs. after eating	....	0.154	....	0.143		
3 hrs. after eating	0.257	0.200	0.137	0.156	0.222	0.333
4½ hrs. after eating	....	....	....	0.154		

A test diet of 200 gm. bread and 100 gm. lung was fed on the six days mentioned, without glycosuria. November 9 and 27 were rest days. On November 10, 11 and 18 exercise was begun immediately after feeding, and resulted in lower blood sugar curves than on the control days. On November 12 exercise was given for one hour before feeding and the dog then left at rest after feeding. The blood sugar curve seemed to indicate a beneficial after-effect of the exercise upon assimilation.

July 28 exercise was omitted and there was immediate glycosuria of 6.2 gm. in the ensuing twenty-four hours. July 29 the same diet was taken with exercise without glycosuria. There was the usual curve of hyperglycemia on July 28, while on July 29 the plasma sugar did not go above 0.128 per cent. Exercise thus permitted assimilation of 100 gm. bread, though the weight meanwhile had risen to 12.8 kilos.

As a further control to exclude a spontaneous rise of tolerance both bread and exercise were omitted for a month. Then at an increased weight of 13.6 kilos the addition of 100 gm. bread on August 30 caused glycosuria of 0.4 per cent. in 761 c.c. urine, increasing the next day to 1.2 per cent. in 724 c.c. With exercise the sugar excretion was halved on September 1 and absent September 2.

The dog was strong and fond of running and by harder exercise it was possible to increase the bread to 150 gm., though the weight rose gradually, and traces of glycosuria were present whenever the exercise was relaxed a little. By September 28 the weight had reached 14.8 kilos and the bread was increased to 200 gm. Traces of glycosuria were present during the ensuing week and were stopped by increasing exercise, so that the dog spent the greater part of every day on the treadmill. Meanwhile much of the lung of the diet was left uneaten and the weight by October 20 had fallen to 13.3 kilos.

TABLE XXIV.—DOG. B2-88. MODERATELY DIABETIC. COMPARISON OF EXERCISE, EXERCISE WITH INTRAVENOUS GLUCOSE INJECTIONS, 1 GM. PER KGM. PER HR., AND INTRAVENOUS GLUCOSE INJECTIONS ALONE.

Time.	Plasma sugar, per cent.			Hemoglobin, per cent.			Urine volume, c.c.			Urine glucose, per cent.			Rectal temperature, °F.		
	I.	II.	III.	I.	II.	III.	I.	II.	III.	I.	II.	III.	I.	II.	III.
Before injection	0.143	0.161	0.118	..	..	107	..	..	..	0	0	0	..	..	101.6
¼ hr. after 1st injection	0.156	0.200	0.200	..	..	93	..	15	120	..	0	0	..	..	101.1
¼ hr. after 2d injection	0.189	0.200	0.200	..	..	91	..	10	64	..	0	0	..	..	101.0
¼ hr. after 3d injection	..	0.164	0.232	..	..	94	..	4	73	..	0	0	..	..	101.2
¼ hr. after 4th injection	0.161	0.147	0.192	..	..	85	10	26	100	0	0	0	..	..	101.6
¼ hr. after 5th injection	..	0.126	0.200	..	..	82	..	5	106	..	0	0	..	..	101.6
¼ hr. after 6th injection	..	0.118	0.200	..	..	89	..	17	64	..	0	0	..	..	101.4
¼ hr. after 7th injection	..	0.112	0.200	..	..	91	..	20	90	..	0	0	..	..	101.5
¼ hr. after 8th injection	..	0.121	0.128	..	..	..	..	20	110	..	0	0			
¼ hr. after 9th injection	..	0.105	0.112	..	..	..	..	20	117	..	0	0			
¼ hr. after 10th injection	..	0.133	0.121	..	..	..	..	16	..	..	0				

I, Nov. 29, 1915, exercise fasting; II, Dec. 2, exercise with intravenous glucose injections, 1 gm. per kgm. per hr.; III, Dec. 7, intravenous glucose injections, 1 gm. per kgm. per hr.

Exercise was then stopped and a diet begun of 200 gm. bread, 100 gm. lard and only 200 gm. lung. November 5, at a weight of 14.1 kilos, glycosuria appeared (0.34 per cent. in 780 c.c. urine), and increased on the following day to 0.95 per cent. in 620 c.c. It was abolished by a fast day on November 7. This control proved that the preceding absence of glycosuria had not been due to the reduced protein intake.

Exercise was then omitted except for a series of tests, most of which are shown in Tables XXIII and XXIV and Chart IV. It was evident from these that exercise retained its power to diminish hyperglycemia even after long usage.

Subsequently, without exercise, on a diet of 200 gm. bread and 100 gm. lung with such lard as might be eaten, there was gradual increase of weight without glycosuria but with increasing hyperglycemia. April 10, 1916, at a weight of 16 kgm., glycosuria appeared and rapidly increased in a more threatening manner than before, reaching 4.5 per cent. The heaviest exercise was then unable to stop it, though it ceased promptly with omission of bread or with single fast days. April 22 to 30 glycosuria was kept absent by carbohydrate-free diet in order to give a fresh start, but with addition of the 200 gm. bread there was again heavy glycosuria in spite of exercise.

Beginning May 5 exercise and reduction of the bread ration to 100 gm. kept glycosuria absent and reduced the weight to 14.3 kgm. Nevertheless, glycosuria appeared on May 14 and 15, was temporarily checked by increased exercise, but reappeared May 18 and resisted exercise.

Exercise and carbohydrate were then omitted, and on regulated diet the weight was gradually reduced by August 16 to 13.2 kilos. Though the tolerance at this weight had formerly been so high, marked glycosuria now resulted, even after the long interval allowed for recuperation, from the addition of as little as 25 gm. bread. With exercise this glycosuria was promptly abolished and remained absent on a diet of 200 gm. lung, 100 gm. suet and 25 gm. bread until September 12, when it reappeared at a weight of 13.6 kilos.

Bread was then omitted and glycosuria stopped, but hyperglycemia continued notwithstanding exercise. October 18, though the weight had fallen to 12.8 kilos, the increasing hyperglycemia and beginning of acidosis gave warning that the diabetes had reached a dangerous stage. The experiment was therefore ended and an attempt made to save the animal. It proved impossible to restore tolerance for any living diet, and death finally occurred February 25, 1917, at a weight of 8 kilos.

This experiment had been planned for testing the practical benefits of exercise in clinical treatment. It showed (1) that

exercise favors carbohydrate assimilation even over long periods, especially in mild diabetes; (2) that it loses its effectiveness not with time but with increasing severity of the diabetes; (3) that it can atone to some extent for indiscretions in diet and weight but cannot safely be used as a substitute for dietary restriction, and the attempt to force the diet to the utmost and burn up the surplus calories with exercise ends finally in disaster.

Conclusions. 1. The influence of exercise on carbohydrate assimilation was traced from the normal through various stages of impairment. A rise of plasma sugar, presumably representing increased transportation, ordinarily accompanies exercise in the normal animal, and the assimilation for test doses of glucose is increased. In mild diabetes, when there is a tendency to abnormal hyperglycemia from defective assimilation of carbohydrate, exercise markedly diminishes the hyperglycemia and glycosuria and facilitates utilization. This power of exercise to improve assimilation applies to the glucose formed from protein diets or body stores as well as from preformed carbohydrate. It does not depend upon the febrile temperatures which attend heavy exercise in dogs, for equal results were obtained in human patients without important elevations of temperature. It is not lost with long usage but becomes less as the diabetes becomes more severe. At a certain advanced stage exercise is unable to modify hyperglycemia or glycosuria. Beyond this, in the extreme forms of diabetes in partially depancreatized animals and in totally depancreatized animals, the extra mobilization of sugar by exercise results in an actual increase of glycosuria and of the D:N ratio.

2. With regard to diabetic theory, these results seem to indicate: (*a*) That the increased metabolism of exercise does not impose an added strain upon the internal pancreatic function; (*b*) that the combustion of food materials through the increased muscular metabolism and mass resulting from exercise is a definite relief to the internal pancreatic function as compared with the accumulation of such materials through inactivity; (*c*) that the internal pancreatic secretion is nevertheless an indispensable intermediary in such combustion, and that exercise merely enables the muscles to make more active use of such quantity of this secretion as is available to them but cannot compensate when this quantity falls below the necessary minimum.

3. For purposes of practical treatment the combustion of food by exercise is preferable to its deposit in the body, but exercise cannot replace dietary restriction or permanently atone for excessive diets. The fundamental value of exercise is probably as a form of undernutrition. The combustion of calories by exercise, however, is not as beneficial as omitting them from the diet, and loses its potency at a stage when dietetic undernutrition is still effective.

Impairment of sugar utilization by exercise occurs only in the extreme stages of diabetes, but in human patients the nervous and systemic influences must also be considered. With any important degree of undernutrition heavy exercise involves undesirable fatigue and strain, but light exercise aids health. Rest is necessary in the severest cases. In the clinical application, therefore, dependence for the actual control of the diabetes is placed upon diet, and exercise is limited to the requirements of comfort and hygiene. The thorough dietetic treatment thus involves two changes from former practice: on the one hand heavy exercise as advocated by the earlier clinicians for burning up surplus sugar is discouraged; on the other hand the hygienic benefits of lighter exercise are made available to many patients to whom exercise was formerly forbidden.

REFERENCES.

1. Benedict, F. G., and Smith, H. M.: Jour. Biol. Chem., 1915, xx, 243.
2. Lusk, G.: Jour. Biol. Chem., 1915, xx, 61.
3. Rockefeller Institute Monograph No. 11, 1919.
4. Moraczewski, W.: Berl. klin. Wchnschr., 1915, lii, 1038; Biochem. Ztschr., 1915, lxxi, 268.
5. Mackenzie, G. M.: Proc. Soc. Exp. Biol. and Med., 1916, xiii, 130; Arch. Int. Med., 1917, xiv, 599.
6. Allen, F. M.: Boston Med. and Surg. Jour., 1915, clxxiii, 743.
7. Allen, F. M., and Wishart, M. B.: Jour. Biol. Chem., 1920, xlii, 415.
8. Allen, F. M.: Jour. Exp. Med., 1920, xxxi, 381.

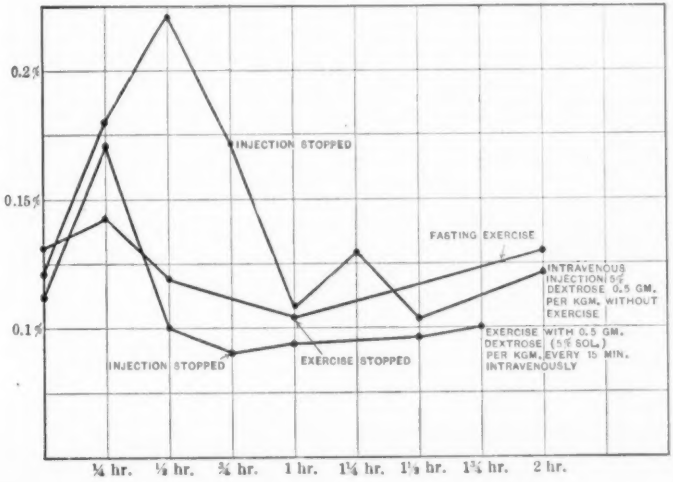


CHART I.—Dog C3-54. Normal. Weight 19 kgm.

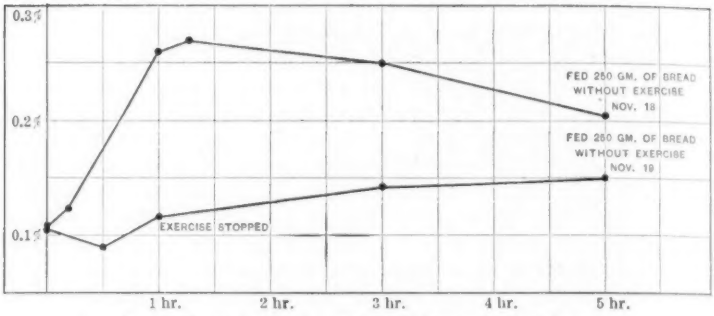


CHART II.—Dog B2-63. Weight 30 kgm. Mild diabetes.

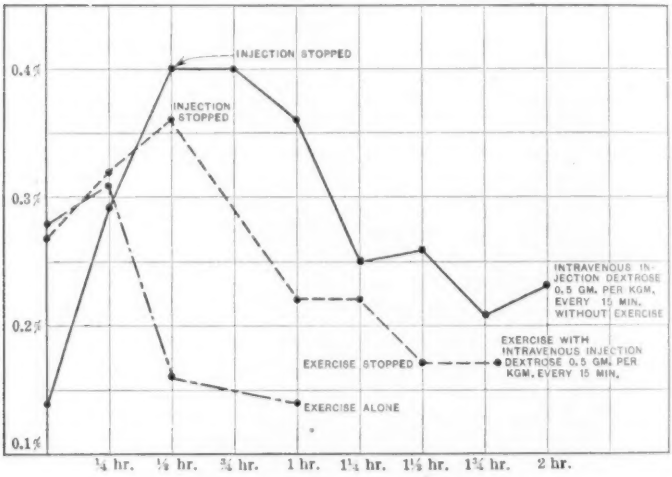


CHART III.—Dog B2-79. Mildly diabetic.

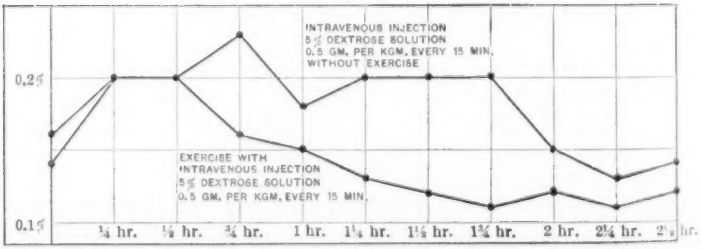


CHART IV.—Dog B2-88. Moderate diabetes.

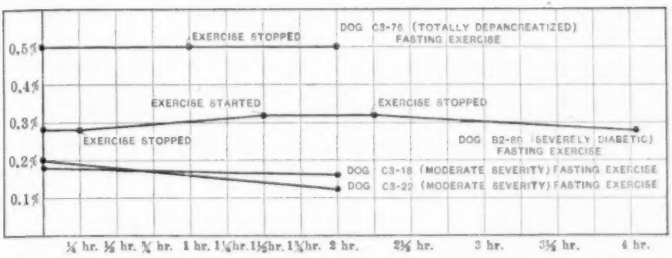

DOG C3-76 (TOTALLY DEPANCREATIZED) FASTING EXERCISE
EXERCISE STOPPED
0.5%
0.4%
EXERCISE STARTED
EXERCISE STOPPED
0.3%
DOG B2-80 (SEVERELY DIABETIC) FASTING EXERCISE
EXERCISE STOPPED
0.2%
DOG C3-18 (MODERATE SEVERITY) FASTING EXERCISE
DOG C3-22 (MODERATE SEVERITY) FASTING EXERCISE
0.1%
½ hr. ½ hr. ¾ hr. 1 hr. 1¼hr. 1½hr. 1¾hr. 2 hr. 2½ hr. 3 hr. 3½ hr. 4 hr.

CHART V.—Exercise in severely diabetic dogs.

RETENTION OF PROTEIN DURING DIET REDUCTION TO RELIEVE THE GLYCOSURIA IN DIABETES MELLITUS.

BY R. L. FENLON, M.D.,

IOWA CITY, IOWA.

(From the Laboratory of Chemical Research of the Department of Internal Medicine, State University of Iowa.)

THERE was recently reported from this clinic a dietetic treatment of diabetes mellitus.[1]

The procedure is essentially the maintenance of the protein intake at a moderate level, the restriction of the fat and the relatively rapid reduction of the carbohydrate until the patient's glycosuria disappears. The carbohydrate tolerance is then built up by a gradual increase in the carbohydrate intake (starvation days are dispensed with). The treatment is controlled by daily twenty-four-hour urine analyses and frequent blood analyses.

Some 15 cases were reported in the earlier paper. At the present writing 40 cases (63 admissions) have been treated under this method of protein retention in the diet.

The mortality was 5 per cent. (2 cases). One of these two was a case of carcinoma of the prostate gland, with retention of urine and a mass in the left lower abdomen; the patient died the second day postoperative. The other case was a refractory patient who had been in the hospital for three admissions. At no time would he follow the prescribed diet, and died of diphtheria and a lung abscess; pure culture of Klebs-Loeffler bacilli were obtained from the bronchi and abscess cavity at necropsy.

With the exception of one case, which showed a slight amount of acetone, all cases were sugar- and ketone-free upon discharge.

There is a gradual reduction in acetone and diacetic acid from the beginning of dietary treatment.

[1] Fenlon, R .L.: Diet Reduction with Retention of Protein to Relieve Glycosuria in Diabetes Mellitus, Bost. Med. and Surg. Jour., February 12, 1920, No. 7, clxxxii, 168–171.

All but one of the cases coming under observation a second time have increased in weight.

This method of relieving glycosuria in diabetes mellitus and of subsequently establishing the dietary tolerance has been found applicable to patients of all ages.

General Outline of Treatment. Examination of the patient.

(*a*) When a case is admitted a careful history is taken by the medical intern in charge, special note being made as to the age of the patient, the duration of the symptoms and the severity of the disease, the complications, if any are present and the diet followed before entrance to the hospital.

(*b*) A complete physical examination.

(*c*) Routine blood and urine analyses are made, *i. e.*, blood sugar and fat; urine sugar acetone and diacetic acid.[2]

According to the data collected in the above-mentioned examination the treatment to be followed in the particular case is determined, and each case is classified a severe, moderate or mild type to facilitate its subsequent treatment.

The severe type includes all patients under twenty-one years of age, even though the diabetes may appear mild; all cases showing the three cardinal urinary findings acetone, diacetic acid and sugar; cases having a hyperglycemia accompanied by a hyperlipemia and those showing a tendency toward coma. Into the group of moderate diabetics fall all those showing sugar and acetone in the urine or having hyperglycemia, with slight or no hyperlipemia.

The mild type includes cases showing only sugar in the urine and having a hyperglycemia, with only slight or no hyperlipemia.

Method of Establishing a Carbohydrate Tolerance. While under treatment (after the glycosuria has been overcome) the amount of carbohydrate is raised each day, particular care being exercised to avoid the reappearance of sugar in the urine. In this series a "break" (glycosuria) occurred in 7.5 per cent. of the cases. The reason for avoiding a "break" is that a patient going out of the hospital without glycosuria appearing when the arbitrary carbohydrate tolerance is reached has a more stable outlook than one who is discharged with a weakened sugar function as shown by the recent "break."

It is evident that the most of these cases have been sent out on what might be termed an arbitrary carbohydrate tolerance; in other words, on a daily intake which is lower than the actual tolerance, a margin of safety is thus provided. The factors entering into the determination of this are the specific gravity of the urine, the severity of the case, the amount of urine passed in twenty-four hours and the hunger as expressed by the individual.

[2] Blood fat by Bloor's method. Blood sugar by Benedict Myers's method. Acetone by Rothera's Reaction. Diacetic acid by Gerhardt's method.

The specific gravity reading varies in each case at the time the patient is sugar-free. As the dietary treatment progresses the specific gravity generally decreases somewhat below this point. As the carbohydrate intake increases toward the arbitrary tolerance the specific gravity gradually approaches the level of the first sugar-free reading. In most cases it is not advisable to further increase the carbohydrate intake after the specific gravity reading rises to this level.

The severity of the disease as shown by the urinary and blood findings at the onset of the treatment and deductions drawn from the individual case give an approximate knowledge of the patient's tolerance.

The daily amount of urine passed also is an indication to a slight extent. As an example, when the succeeding daily amounts fluctuate markedly in the following manner, 1200 c.c., 2100 c.c., 1150 c.c., 1900 c.c. it is well to be cautious with the carbohydrate increase.

The final and most important point is the hunger of the patient. It is not advisable to raise the diet in carbohydrate when the patient maintains that his food intake is sufficient. No definite caloric intake (according to the weight of the individual) is followed in the treatment at this hospital. The final diet is adjusted to suit the wants of the patient. In a very few cases the diet was increased after the hunger was satisfied and glycosuria resulted.

Fehling's test for sugar in the urine as used here follows: Equal amounts of "A" and "B" solutions are mixed in a test-tube (2 or 3 c.c. of each) and boiled in a water-bath. One c.c. of urine is added and the boiling continued. There may be no direct reduction when hot, but the reduction may appear when the tube and contents are set aside to cool.

Dietary Treatment Used to Relieve Glycosuria in Severe Cases. In cases six or seven years old 35 to 40 grams of protein per day are given, the amount being increased with the age and size of the patient. An adult receives 70 to 80 grams per day. This protein level is maintained throughout the patient's stay at the hospital unless a higher caloric diet is desired upon discharge; at that time the protein allowance may be increased.

Fat is eliminated from the diet on the day of admission and is the last constituent to be replaced.

The daily carbohydrate intake in these cases is placed at from 130 to 140 grams and is maintained at this level for two or three days.

Accessory treatment at the onset consists in bed-rest, retention of body heat with blankets, forced warm drinks (fat-free broths, weak tea or coffee and warm water). The rate of forcing these fluids depends upon the amount of urine eliminated in twenty-four hours, the object being to keep the fluid intake at a level slightly greater than or equal to the fluid output.

To summarize: The protein is kept at a constant relatively high

level (35 to 40 grams in children, 70 to 80 grams in adults), the fat is practically eliminated and the carbohydrate is at 130 to 140 grams. The next step in the diet reduction is the diminution of the carbohydrate 10 or 15 grams a day until the patient's glycosuria is relieved. If the glycosuria does not disappear when but 10 grams of carbohydrate per day are given the treatment as outlined in a previous paper is followed.[3]

"Third Step. If glycosuria is still present add 50 to 100 grams of oatmeal to the diet for two days.

"Fourth Step. If glycosuria persists, repeat the diet used just preceding the oatmeal days, lowering the proteins one-third. Keep the patient two days on this diet if necessary.

"Fifth Step. If not aglycosuric, starve, giving only fat-free broths and water for a two-day period.

"Sixth Step. If necessary revert to the oatmeal diet for two days and again starve."

During the period of low caloric intake the calories may be increased by the use of alcohol. Alcohol (as whisky) has not interfered in any way with the establishment of a sugar tolerance in this series of cases.

When the patient becomes aglycosuric (at which time he is generally diacetic acid-free and showing less acetone in the urine) the carbohydrate is increased 1 gram per day in the young or 3 grams per day in adults. The fat is gradually increased when the carbohydrate totals 18 to 20 grams, but is kept at least 10 grams lower than the carbohydrate until the laboratory tests indicate that the carbohydrate tolerance has been reached. The fat at that time may be gradually raised to the same level as the protein or even 5 grams higher. The allowance of fat in the final diet is checked by a blood fat. The patient is then instructed to return to his home for a period of two or three months since this diet, as a rule, provides sufficient calories for the time being and will give a rest to the metabolic mechanism.

At the end of this time a return to the hospital is advised when a readjustment of the diet is made, the amount of carbohydrate being increased and the fat or protein changed if necessary.

The long period of diet reduction in this type of diabetes is invaluable for overcoming the hyperlipemia. One case treated as outlined above came in with a blood fat of 1.14 per cent. and was discharged with a blood fat of 0.596 per cent. A second case upon admission showed 2.28 per cent. blood fat; three weeks later 1.14 per cent., a reduction of $\frac{1}{2}\frac{1}{5}$ of the hyperlipemia was noted, and upon discharge the blood fat had been reduced to 0.91 per cent. Other cases with less marked hyperlipemia had a normal blood fat upon discharge. These cases all had negative urines upon discharge, *i. e.*, neither sugar, acetone nor diacetic acid was present.

[3] Loc. cit.

Case History and Chart of Mr. F. L. Clinical Number, 7230.

Complaints. Excessive urination and weakness of the calves and wrists.

Social History. White male, aged fifty years; farmer. No venereal history.

Family History. Negative.

Past Medical History. Digestive system: Has always had a very good appetite. His wife often said that he ate too much. Always drank lots of water. Occasionally some belching and heartburn. Otherwise negative.

Present Illness. Began about May, 1919, with nocturnal frequency and excessive twenty-four-hour urine. The urine looked like salt water. Had to void five or six times at night. He could eat like a trooper. Had difficulty in satisfying his thirst, went to a physician and was diagnosed diabetes. Later went to another physician who made the same diagnosis and placed the patient on a diet of eggs, fish, meats and fats, but no sweets. Advised the patient to eat fats and to drink cream. Could not follow this diet longer than six months. Began to be a little deaf nine months ago and has had trouble with vision. At present complains of weakness in the calves of the legs and wrists and excessive urination. Best weight, 180 pounds. Present weight, 147 pounds.

Day.	Sugar.		Acetone.	Diacetic acid.	Protein	Fat.	Carbohydrate.
	Per cent.	Gm.					
1	6.0	178	++++	+++	82	8	123
2	5.1	132	+++	++	84	7	141
3	6.0	175	+++	++	80	5	133
4	5.4	142	+++	++	88	19	110
5	5.7	166	++	++	90	15	100
6	5.4	122	++	++	85	12	88
7	5.4	143	++	+	85	8	81
8	5.1	109	++	+	85	8	70
9	3.3	101	++	+	85	10	58
10	2.0	73	++	tr.	85	13	50
11	1.9	77	++	tr.	82	19	40
12	1.3	57	++	s. tr.	85	8	31
13	1.0	44	+	v. s. tr.	85	8	27
14	0.7	22	tr.	v. s. tr.	80	7	21
15*	0.2	6	s. tr.	v. s. tr.	84	7	16
16	0.5	28	s. tr.	v. s. tr.	86	6	14
17	0.4	24	s. tr.	v. s. tr.	80	6	15
18	0.2	11	s. tr.	v. s. tr.	83	10	9
19	0	0	v. s. tr.	0	81	6	8
20	0	0	v. s. tr.	0	80	7	10
21	0	0	v. s. tr.	0	83	9	12
22	0	0	0	0	83	8	15

* 4 P.M. urine specimen was sugar-free. Sugar (by mistake) was served with evening meal.

Tr. = trace. S. tr. = slight trace. V. s. tr. = very slight trace.

Blood on first day = sugar, 0.454 per cent.; fat, 2.28 per cent.

Physical Examination. Mucosa of mouth and throat is red and dry. Tongue is dry and fissured. Acetone odor to breath. Skin dry and desquamating. Muscles everywhere atrophied and show myoidema. Otherwise negative.

Laboratory Findings. Serum Wassermann negative.

Urine examination: Specific gravity, 1038. Sugar, 6 per cent. Acetone, ++++.

Diacetic, +++ (blue-black).

Blood: Sugar, 0.454 per cent.; fat, 2.28 per cent.

Blood count normal.

Patient was seen again six weeks after discharge, active in farm work and had gained 12 pounds in weight.

The Treatment Followed in the Moderate Type of Diabetes. 80 to 90 grams of protein are given. This amount is not changed except just before discharge, when it may be increased if so desired; 12 to 15 grams of fat daily are allowed in order that the diet may be more palatable. The same amount of carbohydrate as protein is included in the diet. As an example the diet at the beginning of the treatment will be 90 grams protein, 15 grams fat and 90 grams of carbohydrate.

The carbohydrate is then reduced 15 to 20 grams daily until the urine is sugar-free. The carbohydrate is then increased 5 to 8 grams daily until the tolerance is reached. When the diet contains 50 grams or more of carbohydrate the fat is increased 10 to 15 grams per day until the total amount is not more than 10 grams above the next highest constituent (either protein or carbohydrate).

The treatment is varied as follows in cases with nephritis: In adult cases with nephritis the protein is kept at 60 grams daily. The reduction of the carbohydrate from 90 to 100 grams is made slowly, *i. e.*, 10 grams daily, until the patient is aglycosuric. Fat and carbohydrate are increased as above.

Two cases of diabetes and nephritis associated with gangrene have been treated in this series, and in both instances the gangrene cleared up before the patient's discharge from the hospital.

Treatment Followed in Mild Type. Protein and the carbohydrate are placed at 100 grams daily; fat at 20 to 30 grams.

The carbohydrate is halved daily until the urine is sugar-free and is then increased 10 grams per day until the tolerance is reached. When the carbohydrate reaches 60 grams the fat is added 25 to 30 grams daily until the total amount is not over 15 grams higher than the next highest constituent of the diet.

Case History of Mr. O. L. Clinical number, 6999.

Entrance Complaint. Poor vision and inability to hold his urine.

Social History. White male, aged sixty-two years farmer. No venereal history.

Family History. Negative.

Past Medical History. Malaria at age of twelve years. Typhoid at thirty-six. Thirty-two boils on the back of his neck and in his

hair three years ago. Swelling of the ankles during the day for the past two years. Good deal of cramping of the muscles of the legs and thighs the past seven or eight years. Appetite always very good. For the past twelve years has had spells of excessive thirst, and has never missed getting up from two to six times to urinate at night. Often wets his clothes. Poor sleeper the past five or six years. Has been seeing double lately. Has staggered a little, assigned to weakness of the legs.

Present Illness. Inability to hold urine began about twelve years ago and was gradual in its development. Worse at times, especially when he would get thirsty and drink a lot of water. Would have to get up at night to urinate and passed one to two gallons of urine in twenty-four hours. Appetite always good, but has had a special craving for sweets. Often noticed that bees would gather and apparently feed on his urine. For the first three years he used bran bread, and this seemed to help a good deal. Sugar was found in the urine and the patient told that he had diabetes. Has eaten nothing that he knew contained starch or sweets for the past twelve years, excepting pies; he, however, uses sugar in tea and coffee. Always had a preference for fat meat. Noticed that he was getting weaker about two years ago. Skin is dry but never itched. In July, 1919, the patient's vision began to fail. Saw double. Seemed to have a smoky scum over the left eye and could only see with this eye when he looked sideways. Weighed 270 pounds when thirty years old. Maintained about the same weight until he was forty. Lost weight up to fifty (onset of present illness). Present weight, 212 pounds.

Physical Examination. Arcus senilis marked in both eyes. Pupils react to light and accommodation. Left pupil slightly oval in shape. Definite Romberg test. Misses heel to knee test. Walks with a wide base. Ataxic. Knee-kicks and tendo achillis only present on reinforcement. Bilateral neuritis of the nervus cochlearis. Diabetic retinitis.

CHART OF TREATMENT OF MR. O. L.

Day.	Sugar.		Acetone.	Diacetic acid.	Blood.		Protein.	Fat.	Carbohydrate.	Calories.
	Per cent.	Gram.			Sugar.	Fat.				
1	2.2	20	0	0	0.263	0.857	94	6	105	850
2	1.1	13	0	0	....	....	94	8	90	808
3	0.0	0	0	0	....	....	90	16	47	692
4	0.0	0	0	0	....	....	94	12	36	628
5	0.0	0	0	0	....	....	93	23	62	827
6	0.0	0	0	0	....	....	97	31	75	967
7	0.0	0	0	0	....	....	98	43	84	1155
8	0.0	0	0	0	....	....	98	66	80	1306
9	0.0	0	0	0	....	....	96	88	90	1536
10	0.0	0	0	0	....	....	98	108	100	1764
11	0.0	0	0	0	0.133	0.732	100	110	100	1790

Laboratory Findings. Blood count was negative except for an eosinophilia of 3 per cent. Serum Wassermann negative on two tests.

Weekly Fast Days. Weekly fast days do not enter into the treatment used either at the University Hospital or that subsequently followed by the patients in their homes.

The purpose of this treatment is to produce as stable a carbohydrate metabolism as possible. This is done by establishing the tolerance with small increments, 1 to 2 grams per day in all severe cases. In our opinion weekly fast days may defeat this purpose, in that the withdrawal of the carbohydrate and the rapid resumption of the load may tend to strain the sugar mechanism. Out of 38 cases so treated 8 have returned for an increase of the carbohydrate in the diet. None of these 8 cases have shown glycosuria while at home for periods of three to five months and the tolerance of all upon return has been set at a higher level.

Cases are advised to return to the hospital should they desire an increase in their diet; however, they are asked not to return in less than two months unless something untoward develops.

CHART OF RETURN CASES

Case.	Diet first discharge.				Diet second discharge.				Diet third discharge			
	Pro.	Fat.	Cho.	Cal.	Pro.	Fat.	Cho.	Cal.	Pro.	Fat.	Cho.	Cal.
1	60	90	50	1250	85	85	75	1405	85	85	85	1445
2	65	75	45	1115	60	75	75	1215				
3	90	90	40	1330	100	100	80	1620				
4	40	35	31	600	70	70	50	1110				
5	70	90*	60	1330	100	115	85	1775				
6	100	100	85	1640	110	120	105	1940				
7	100	110	100	1790	100	100	115	1760				

* Discharged under previous method of treatment.

Case 1. Nineteen years old, slightly under weight. During first admission she "broke" on 40 gm. of carbohydrate.

Case 2. Slight build, no complaint of hunger.

Case 3. Tall, slender, "broke" on 46 gm. of carbohydrate (first admission).

Case 4. Boy, aged six years. Has gained in weight and plays with other children.

Case 5. Travelling man, aged thirty-three years.

Case 6. Male, aged twenty years. Plays basket ball on a town team, trapped and hunted between his two admissions and gained ten pounds in weight.

Case 7. See case report No. 6999.

Results from High Fat Diets. Some cases before entrance to the hospital had lived upon a diet rich in fats. The difficulties encountered while treating such cases suggested the following conclusions:

1. A longer period of time with a continuous low calorie diet was necessary to overcome the glycosuria and ketonuria.

2. Although the tendency of a high fat diet (especially with a low carbohydrate intake) to produce acidosis is well known; too little attention is paid to this point by the general practitioner. Many patients are advised by their physician to limit their sugar, bread, potato and starch intake, but no mention is made of the fat intake; in fact a few cases (see case report of Mr. F. L.) have been told to increase their fat consumption by eating cheese, butter, nuts, etc., and drinking cream.

3. High fat diets appear to cause a decrease in the carbohydrate tolerance; that is, with long-continued, high fat ingestion the carbohydrate seemingly cannot be placed at as high a level as the case should tolerate.

Foci of Infection. Demonstrable foci of infection such as diseased teeth, tonsils, etc. are removed during the patient's stay in the hospital, the diet being established before operation. The daily food intake (that is only the fat and carbohydrate) is reduced on the day of the operation and replaced slowly as the urinary picture clears.

Oatmeal Treatment. Oatmeal, because of its slow absorption and high potassium content, has been used recently in a few instances as the principal carbohydrate of the food intake during the diet reduction. Two-thirds of the daily carbohydrate is given as oatmeal. Results in a case follow: The first urine specimen received from this patient contained 12.5 per cent. of sugar. The urine was sugar-free after four days of diet reduction. Treatment was completed in sixteen days and then his tolerance was set at 100 grams of protein, 100 grams of fat and 75 grams of carbohydrate.

Case History of Mr. M. G. Clinical Number 7598.

Entrance Complaint. Diabetes.

Social History. White male, aged twenty years; single; farmer. No venereal history.

Family History. Negative.

Past Medical History. Light attack of influenza in the fall of 1918.

Present Illness. Began about five weeks ago with polyuria, which gradually increased until in two weeks he was passing thirteen pints of urine in twenty-four hours. He developed a ravenous appetite and drank large quantities of water. Two weeks before admission he consulted a physician, who found sugar in his urine. The diet recommended was to omit sugars and syrups and to reduce bread and potatoes to half the usual amount. After this the total twenty-four-hour urine decreased to an average of seven to nine pints. Weight two months ago was 158 pounds and at present 138 pounds. He has felt drowsy in the daytime during the past two weeks.

Physical Examination. Patient is a slender, fairly well-nourished, white male of twenty. Face is flushed. Skin on the body is dry. Tongue is semi-moist. Otherwise negative.

Laboratory Findings. Serum Wassermann negative on two tests. Blood count was negative except for an sosinophilia of 5 per cent. Urine: Specific gravity, 1052. Sugar, 12.5 per cent. Acetone and diacetic negative. Blood sugar, 0.270 per cent.

Some Dietary Regulations Which Are Deemed Advisable to Incorporate in the Treatment. 1. Milk and orange are to be excluded from the diet in severe cases. Milk because of its prompt assimilation is given only when the carbohydrate tolerance is above 30 grams; exception to this is made in cases of children. Orange tends to cause a glycosuria before the normal tolerance of the particular case is reached. In a few instances the feeding of orange caused a glycosuria which upon withdrawal of orange from the food was relieved and the carbohydrate was increased to a higher level without the reappearance of sugar in the urine. Grapefruit and rhubarb are used in the place of orange without the danger of causing glycosuria prematurely.

2. No cane sugar is to be given as such, regardless of the tolerance. Saccharin is to be used for sweetening.

3. The food is to be divided equally among the three meals of the day, *i. e.*, one-third of the protein, one-third of the fat and one-third of the carbohydrate are to be included in the breakfast, in the dinner and in the supper.

4. Bananas are not to be included in the diet when the tolerance, is less than 90 grams of carbohydrate.

Instructions Given to the Patient for His Use after Leaving the Hospital. While the patient is in the hospital he receives a course of instructions on his diet in which he becomes familiar with the food constitutents, protein, fat and carbohydrate, both as to the physiologic action, source and calorific value.[4]

After the patient has become familiar with the food value of most of the common food materials, he is taught to calculate a day's diet. Great stress is put upon the equal division of the food among the three meals of the day, *i. e.*, one-third of the protein, one-third of the fat and one-third of the carbohydrate at each meal.

Six days' diet are given to the patient when he leaves, and he is instructed to live only on a weighed diet. Since one-third of his food allowance for the day is given in each meal there can be a variety of the day's diets; for a breakfast of one day and a dinner of another and a supper of a third day can be taken with no danger of exceeding his tolerance. The patient is taught to substitute one food for another, so that he may vary his diet as the foods in season vary, and he is more content to live on a prescribed diet too when he can make slight changes to suit his individual taste. In order that no difficulty may arise in regard to the use of a balance for weighing the food, he is taught to weigh out foods on the balance that he is to use

[4] Government Bulletin No. 28, Chemical Composition of American Food Products has been found helpful.

after leaving the hospital. This instruction enables the patient to calculate his own diet if he so desires.

The doctor in charge gives the patient instructions in the qualitative urine tests for sugar and diacetic acid, and the patient is instructed to test the urine for sugar each day. He is told to use but 1 c.c. of urine in performing Fehling's test and is shown the various phases of reductions with this test when sugar is present, green, yellow and red. Instruction is given to reduce the carbohydrate of the diet slightly when a green or yellow reaction results and when the urine is again sugar-free to gradually return to the former level. He is instructed to return to the hospital if the reduction is persistently red. In case of an infection such as a severe cold, tonsillitis or other condition with increased temperature, the patient is advised to test his urine for the presence of diacetic acid with the ferric chloride solution, and if he finds the test to be positive to reduce the fat in his diet until the diacetic disappears, when he may gradually increase the fat until the former amount is being taken.

THE BACTERIOLOGY OF THE FASTING STOMACH AND DUODENUM: AN EXPERIMENTAL STUDY BASED ON THE FINDINGS IN THIRTY DOGS.

By Peter H. Poppens, M.D.,
CHICAGO, ILL.

(From the Pathological Laboratory of the Surgical Department of Rush Medical College.)

Clinically it has long been recognized that the upper portion of the gastro-intestinal canal contains relatively few pathogenic bacteria. Cushing and Livingood[1] found difficulty in recovering microörganisms from the mucous membrane of the stomach, duodenum and even the jejunum as far down as complete emptying of the canal occurred. Kohlbrügge[2] in discussing the autosterilization of the intestinal canal stated that the small bowel either has no bacteria at all or, when it does show them, that they belong to the colon group. On the other hand, as long ago as 1886, Escherich[3] showed that in infants B. coli predominates in the lower portion of the intestinal canal while Bacillus lactis aërogenes is found higher up. Gilbert and Dominici[4] examined the intestinal contents of dogs which were killed three hours after a meal of bread and meat. They found many organisms in the stomach, few in the duodenum and a gradually increasing number down the small bowel. Kendall[5] Hess,[6] Sisson,[7] Torrey[8] and others have obtained similar results.

Various factors enter into the production of this relative "amicrobism" of the upper intestinal tract. The foremost of these is perhaps the bactericidal action of the gastric juice. In 1890, Miller[9] took gastric contents three hours after a meal and incubated it. He found three kinds of bacteria three hours afterward, one kind ten later and none at the end of fourteen hours. Gillespie[10] also has shown that there is a marked decrease in the number of bacteria during the period of digestion.

Many experiments have been made to determine which constituent, or combination of constituents, of the gastric juice is the germicidal factor. Macfayden[11] estimated the maximum antiseptic power of hydrochloric acid by means of gelatin plate cultures. He added known quantities of the acid to the gelatin, but did not determine the percentage of free acid remaining after sterilization. Working with a number of organisms, including Staphylococcus aureus, Bacillus pyocyaneus, Bacillus anthracis and Bacillus typhosus, he found that pepsin alone had no effect. Hydrochloric acid either alone or along with pepsin hindered the growth of all the organisms, its action not being modified by the presence of pepsin. Staphylococcus aureus and Bacillus typhosus were killed by 0.3 per cent., Bacillus anthracis by 0.1 per cent. and Bacillus pyocyaneus by 0.02 per cent.

That organisms do not all show the same resistance to acid, and that combined acid is less bactericidal than free was shown by Gillespie,[10] who attempted to reproduce the conditions present during normal digestion, particularly by adding the acid in a manner similar to that in which it is added during life. He found that with a total acidity of 0.306 to 0.414 and a free acidity of 0.0935 per cent., Staphylococcus aureus was killed in two to three hours; whereas with a combined acidity of 0.684 per cent. the organism multiplied. Bacillus coli was killed in from one to two and a half hours in acidity ranging from 0.234 to 0.511 per cent., part of it being free hydrochloric acid. Fermi[12] added various acids and alkalies to sterilized neutral glycerine agar and obtained results slightly higher than those obtained by Gillespie. In 1915, Broadhurst[13] found that streptococci survived 0.2 to 0.4 per cent. hydrochloric acid for ten to seventy minutes. Recently, Davis[14] found that "gastric juice of normal acidity from man and from rabbits kills hemolytic streptococci in two to five minutes," and that "gastric juice in achylia may not kill them for several hours." He also found that when introduced into the stomach of rabbits in large numbers virulent hemolytic streptococci occasionally pass through and appear in the feces. Further experiments in which the relation of the hydrogen ion concentration to the number and variety of organisms in the gastric contents is determined should be made.

That there is ample opportunity for some organisms to pass unharmed through the stomach is readily seen when one considers the following facts: (1) The acidity does not reach its maximum

until one-half to one and a half hours after digestion begins; (2) liquid food leaves the stomach almost immediately; (3) saliva laden with organisms is swallowed in interdigestive periods; (4) food particles may protect organisms from the action of acid, and finally (5) many bacteria, some of which are pathogenic, as, for example, staphylococci, Bacillus coli and Bacillus typhosus are resistant to a degree of acidity greater than found in the normal stomach during digestion. Cushing and Livingood[1] maintain there is a tendency on the part of the stomach to completely free itself together with the end-products of digestion from even those micro-organisms which are resistant to the gastric juice. In four cases of gastrostomy for stricture of the esophagus where no food had been taken for at least six hours the stomachs were found sterile at operation.

Gilbert and Dominici[4] showed that a sudden reduction in the number of bacteria as the duodenum is reached occurs even during digestion. At one time bile and pancreatic juice were believed to have a bactericidal action, but the experiments of Leubuscher[15] and others have shown that this is very slight if present at all. Yeasts alone are inhibited by bile according to Leubuscher. The dilution of the chyme may be a factor, as pointed out by Gilbert and Dominici. Hess[6] found that a greater or less amount of bile in the duodenum stood in no definite relationship to the number of bacteria present. Cushing and Livingood[1] report a case of complete common duct obstruction, due to carcinoma, in which the duodenum was sterile after six hours' fasting, showing that "amicrobism" of this organ could occur without as well as with the presence of bile.

Duodenal contents have been variously studied in an attempt to establish a definite flora. Gessner[16] examined the duodenal contents of eighteen persons shortly after death and found eight varieties. Bacillus lactis aërogenes, streptococci, Bacillus coli and staphylococci were among those found frequently and in considerable numbers. Hess[6] catheterized the duodenum in infants a few hours old and nurslings from one to six weeks of age. A few organisms, mostly staphylococci and moulds, were found in the infants. Up to one week of age the most frequent organisms in the stomach and duodenum were staphylococci. Bacillus coli was found in the duodenum in only one instance. In children two to six weeks old Bacillus coli were almost invariably obtained from the duodenum and less constantly from the stomach. The samples were taken at a time when the stomach was relatively empty. The flora of the stomach and duodenum was found to be practically the same; only fewer organisms were obtained from the duodenum. Cushing and Livingood found many duodenums sterile after a period of fasting, and believe, therefore, that one should not speak of a definite flora of the duodenum. Sisson[7] examined the bacterial content of the bowel at various levels in puppies fasted from eight to twenty hours. In each instance he obtained a reduction in the number of bacteria

in proportion to the length of the period of fasting, but in no instance was the duodenum sterile. Staphylococci, streptococci and Bacillus coli were the organisms most frequently encountered.

It was early recognized that the number of organisms at any level depends not only upon the period of fasting but also upon the type of diet. The following table is quoted from Gilbert and Dominici[17] and contrasts the difference in number of bacteria between a mixed and a milk diet. His dogs were kept on milk exclusively for two weeks.

	Mixed diet.	Milk diet,
Stomach	50,000	100 organisms per mg.
Duodenum	30,000	50 " "
Ileum	100,000	1300 " "
Large intestine	30,000	1275 " "

The type of diet appears not only to influence the number of bacteria but also to exert a marked influence upon the varieties present. Kendall[5] has shown that on a carbohydrate diet fermentative bacteria replace the proteolytic type—longer, thinner, Gram-positive rods replace the rather stout bacilli seen upon a protein diet. Torrey[8] kept dogs on a regulated diet for a period of seven weeks and examined the intestinal contents at various levels eighteen to twenty hours after the last feeding. On a rice and meat diet a few streptococci and Bacillus welchii were found in the duodenum. When lactose was substituted for rice numerous Bacillus acidophili, a few streptococci and some hydrogen sulphide-forming bacteria were found. Finally, when saccharose was the carbohydrate used a few Bacilli welchii and hydrogen sulphide-forming bacteria were noted. Although Sisson found the same types of organisms throughout the intestinal tract, Torrey, on the other hand, found different organisms at various levels, and points out that "generalizations in regard to the bacterial conditions in the upper levels based on the examination of fecal specimens should be made with caution."

While working with Dr. Gatewood upon the relative efficiency of various cholecystenterostomies, including cholecystogastrostomies, cholecystoduodenostomies and cholecystocolostomies, an opportunity presented itself for making a qualitative study of the flora of the stomachs and duodenums of normal fasting dogs.

Method. Dogs kept on a mixed diet of bread and meat were not fed for fourteen hours previous to the operation. Aseptic technic was used throughout. The opening into the stomach or bowel was made with a clean knife and some of the contents aspirated with a sterile pipette. In this way two to four drops of semiturbid fluid could be obtained. This was inoculated directly into 10 c.c. of 1 per cent. dextrose broth and incubated for eight to twelve hours. Subcultures were then made on blood agar plates, dextrose agar tubes, plain agar slants (anaërobic) and litmus milk. The preliminary period of incubation was decided upon after it was found that subcultures made immediately sometimes remained sterile;

whereas inoculation from the same broth tube after eight to twelve hours gave an abundant growth. After twenty-four to forty-eight hours colonies were picked from the blood agar plates and from the dextrose agar tube for further identification. Bacillus coli were identified by their morphology, Gram's stain and motility, as well as by their growth in the various media (1 per cent. dextrose, lactose and saccharose agar tubes, litmus milk, Dunham's peptone and potato).

Gram's stains were made of a number of direct smears, but in the stomach these usually revealed only yeasts, and a few if any bacteria. In the duodenum no organisms at all or only isolated ones could thus be demonstrated. This method was therefore abandoned and stains were made of the sediment in the twenty-four-hour dextrose broth tubes and from the growth on four day old anaërobic agar slants. His's capsule stain was made on organisms grown in milk when media reactions made this necessary. All media were +1 acid to phenolphthalein. For blood agar plates ten drops of human blood were added to 10 c.c. of agar. In two cases 2 c.c. of a twenty-four-hour broth culture of Bacillus coli from the duodenum was injected into the peritoneal cavity of a guinea-pig. In each instance death was produced in about twenty hours, the organism being isolated in pure culture from the heart's blood.

In the duodenum Gram-positive organisms not constant in morphology and innocuous to rabbits and guinea-pigs were noted. They sometimes resembled cocci, at other times bacilli, showed a tendency to be arranged in pairs and in cultural characteristics agreed with Enterococcus proteiformis.

STOMACH.

Dog No.	2	3	4	8	9	11	14	15	16	17	18	32	34	35	36	Total.
Number of hours fasting	14	14	14	14	14	14	14	14	14	14	14	20	14	22	22	
Bacillus coli	0	0	+	0	+	0	0	0	+	0	0	0	+	0	0	4
Staphylococci	+	+	+	citreus + aureus	0	+	+	+	+	+	+	0	0	0	+	11
Streptococci	0	+	0	+ green	0	0	+	+ green	0	0	0	0	0	0	0	4
Subtilis group	0	0	0	+	0	0	0	+	+	0	+	+	+	+	+	8
Moulds	+	+	0	0	+	0	0	0	0	0	0	+	0	0	0	4

DUODENUM.

Dog No.	19	20	21	22	23	24	25	28	29	30	31	34	35	36	11	Total.
Number of hours fasting	14	14	14	14	14	14	14	14	14	14	14	14	22	22	14	
Bacillus coli	+	+	0	+	+	+	0	+	+	0	+	+	+	+	+	12
Staphylococci	+	0	+	0	0	0	0	0	0	0	0	0	0	+ aureus	0	3
Streptococci	0	0	0	+	0	0	0	0	0	+ green	0	0	0	+	+	4
Subtilis group	+	+	0	+	0	0	0	0	+	0	0	+	+	+	+	8
Moulds	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Enterococci	..	..	..	..	+	..	+*									

* Pure culture.

While the number of animals examined is not large the uniformity of results is rather striking. It will be seen that in the duodenum, Bacillus coli was found twelve times out of fifteen, after a period of fasting of fourteen to twenty-two hours; whereas in the stomach this organism was found only four out of fifteen times. On the other hand staphylococci, most frequently of the albus variety, were found in the stomach eleven out of fifteen times, and only three times in the duodenum.

Streptococci were found an equal number of times in the stomach and the duodenum. Hemolytic streptococci were not found. Organisms that produce hemolysis were not infrequent, some of the Bacillus coli producing a rather wide zone (4 or 5 mm. in diameter) in twenty-four hours. Two out of the four streptococci isolated produced methemoglobin. In one duodenum Streptococcus viridans was found in pure culture.

Although in some instances immediate plating gave sterile cultures, by the method employed in these experiments no stomach or duodenum was found amicrobic even after the dogs had been fasted twenty-two hours (two cases). This would seem contrary to the results of Cushing and Livingood, who found quite a few sterile duodenums. These authors, however, took only an ordinary loopfull of material and made immediate aërobic and anaërobic plates.

Practically all organisms were facultative anaërobes. Sporeformers in most instances belonged to the Bacillus subtilis group.

Summary. 1. By taking two to four drops of material from the fasting stomach and duodenums of dogs a variety of organisms was invariably found.

2. Bacillus coli was much more frequently found in the duodenum than in the stomach.

3. Non-hemolytic streptococci were rarely found in either stomach or duodenum and hemolytic streptococci not at all.

4. Staphylococci were found in eleven of fifteen stomachs and in but three of fifteen duodenums.

BIBLIOGRAPHY.

1. Cushing, H., and Livingood, L. E.: Experimental and Surgical Notes upon the Bacteriology of the Upper Portion of the Alimentary Canal, with Observations on the establishment there of an Amicrobic State as a Preliminary to Operative Procedures on the Stomach and Small Intestine, Contributions to the Science of Medicine, by pupils of Welch, 1900, p. 543.

2. Kohlbrügge: Der Darm und seine Bacterien; kritisches Referat unter Zuziehung eigener Untersuchungen, Centralbl. f. Bakteriol., 1901, xxx, 10, 70.

3 Escherich, Theodor: Die Darmbakterien des Säuglings, und ihre Beziehung zur Physiologie der Verdauung, Stuttgart, 1886.

4. Gilbert, M. M., et Dominici, S. A.: Recherches sur le Nombre des Microbes du tube Digestif, Comptes rend. de Soc. de Biologie, 1894, ix, 117.

5. Kendall, A. I.: Certain Principles Relating to the Activity of Bacteria in the Intestinal Tract, Their Relation to Therapeutic, Jour. Med. Research, 1911, xxv, 117.

6. Hess, A. F.: Katheterismus des Duodenums von Säuglinge, Ergeb. der Inn. Med. und Kinderheilk., 1914, xiii, 530.

7. Sisson, W. R.: Experimental Studies of the Intestinal Flora, Am. Jour. Dis. Children, 1917, xiii, 117.
8. Torrey, J. C.: The Regulation of the Intestinal Flora of Dogs through Diet, Jour. Med. Research, 1918–1919, xxxix, 415.
9. Miller, W. D.: Die Mikroörganismen der Mundkohle, Leipzig, 1892.
10. Gillespie, A. L.: The Bacteria of the Stomach, Jour. Path. and Bact., 1893, i, 179.
11. Macfayden, A.: The Behavior of Bacteria in the Digestive Tract, Jour. Anat. and Physiol., 1887, xxi, 227.
12. Fermi, C.: Die Mineral und Organischen Sauren, die Alkali, die Alkaloide, Das Jodkali und das Arsensaure Kali zur Differenzierung der Mikroörganismen, Centralbl. f. Bakt., 1898, xxiii, 208, Abth. 1.
13. Broadhurst, Jean: Environmental Studies of Streptococci, with Special Reference to the Fermentative Reactions, Jour. Infect. Dis., 1915, xvii, 277.
14. Davis, D. J.: The Fate of Streptococcus Hemolyticus in the Gastro-intestinal Canal, Jour. Infect. Dis., 1920, xxvi, 171.
15. Leubuscher: Einfluss von Verdauungssekreten auf Bakterien, Ztschr. f. klin. Med., 1890, xvii, 472.
16. Gessner, C.: Ueber die Bakterien im Duodenum des Menschen, Arch. f. Hyg., 1889, ix, 128.
17. Gilbert et Dominici: Action du Regime Lacte sur le Microbisme du Tube Digestif, Bull. de la Soc. de la Biol., 1894, ix, 277.

LEUKEMIA: TYPE DIAGNOSIS BY OXYDASE METHOD OF BLOOD-STAINING.

By George L. Lambright, M.D.,
CLEVELAND, OHIO.

There are two types of leukemia, the lymphatic and myelogenous, the diagnosis of which is based on doubtful clinical and hematological grounds. It is said that in lymphatic leukemia the lymph glands are enlarged out of proportion to the spleen, while in splenomyelogenous leukemia the splenic enlargement is more prominent. This is only true in a certain number of cases. When judgment of type is based on such clinical data, disappointment will often be encountered, due to obtaining blood-findings, which disagree.

In late years more confidence has been placed on the examination of stained blood smear. This is a helpful means, but is uncertain, too, for there are many questions among observers in regard to differentiation between lymphocytes and myelocytes. The simple statement that the myelocytes are granular and the large lymphocytes non-granular is a good working foundation, but the difficulty is in the recognition of the granules by the ordinary methods of staining. There are, fortunately, some blood smears that stain beautifully by a good fresh Wright stain, and no hesitation is made in deciding which is a granular or non-granular cell. Leaving aside the remainder of the findings in a blood examination of leukemia the distinction between the large lymphocytes and myelocytes is of

greatest importance. In order to do this the best plan is to stain all blood smears from cases of leukemia by the oxydase method.

In the use of the oxydase method, alpha-napthol and dimethyl-para-phenylendiamin are brought together in the presence of an oxidizing agent which is present in the leukocytes. An alkaline media is required. When this is done a rapid precipitation of indophenol blue occurs which produces blue granular staining of their protoplasm. The reaction is given by neutrophil, eosinophil and basophil leukocytes and by myelocytes in bone-marrow and leukemic blood. The reaction is not given by lymphocytes nor red blood cells. The method is as follows: Solutions required:

Solution *A*.

95 per cent. alcohol	9 parts
Formaldehyde solution (40 per cent. gas)	1 part

Solution *B*.

Alpha-naphtol (Merck's reagent)	1 gram
40 per cent. alcohol	100 c.c.
Hydrogen peroxide (Must be fresh.)	0.2 c.c.

Solution *C*.

Pyronin	1 gram
Anilin	4 c.c.
40 per cent. alcohol	96 c.c.

Solution *D*.

0.5 per cent. solution of methylene blue (Grubler's BX).

Directions. The films should be fixed by covering with solution *A*. After two minutes this is washed off with water and film flooded with solution *B*. This is washed off and the film is allowed to remain in a dish of running water for fifteen minutes. It is then dried and stained for two minutes with solution *C*. This is washed off with water and solution *D* is poured on and allowed to remain for thirty to sixty seconds. After washing with water the slide is blotted and mounted in neutral balsam.

Results: All myeloid cells, polynuclear myelocytes, transitional and myeloblasts, will show blue granules, while lymphocytes and lymphoblasts will not.

Caution: Solution *B* deteriorates very rapidly and must be made up fresh.

A leukemia case, the physical findings of which were not conclusive, was carefully studied by three separate hematologists. A brief summary of the findings will be of interest, as it shows the different interpretations placed upon cells observed stained by different methods within short periods of time:

A child, aged six years, was first seen October 12, 1919, with chief complaint of weakness. Mucous membranes were pale, a petechial rash that later changed to purpuric spots and general glandular

enlargement was present, including the spleen. The blood findings were as follows:

Red blood cells	2,140,000 Per c.mm.
White blood cells	51,000 "
Hemoglobin	40.0 per cent.

250 cells were counted on a slide stained by the oxydase method with following results:

Polymorphonuclears (neutro)	46.0 per cent.
Large lymphocytes	13.0 "
Small lymphocytes	4.0 "
Myelocytes (neutro)	31.0 "
Mast cells	6.0 "

Many nucleated red cells were seen, the larger number of megaloblastic type. Moderate achromia, polychromatophilia, poikilocytosis and anisocytosis were present.

The blood was examined in another laboratory a few days later which corroborated the diagnosis of myelogenous leukemia and reported the following findings:

Red blood cells	2,400,000 per c.mm.
White blood cells	48,000 "
Hemoglobin	48.0 per cent.
Polymorphonuclears (neutro)	59.4 "
Eosinophils	0.4 "
Large lymphocytes	2.8 "
Small lymphocytes	10.2 "
Transitionals	0.4 "
Myeloblasts	6.4 "
Myelocytes (neutro)	20.4 "

Achromia, anisocytosis, polychromatophilia and poikilocytosis was present. Platelets normal. Six megaloblasts and five normoblasts were seen in making the count of 250 cells.

Three days later another laboratory made an examination of the blood and stained the smear by Wright's method and submitted a diagnosis of lymphatic type from the following findings:

Red blood cells	2,192,000 per cmm.
White blood cells	74,000 "
Hemoglobin	30.0 "
Polymorphonuclears (neutro)	50.0 per cent.
Large lymphocytes	27.0 "
Small lymphocytes	14.0 "
Transitionals	1.0 "
Myelocytes	8.0 "

Irregularities in form were noted with abnormal red cells.

In the last examination it will be noted that a diagnosis of lymphatic leukemia was made from the blood findings. This was based on the finding of myelocytes of vanishing quantity. It is probable the method of staining had a great deal to do with the failure to recognize more myelocytes, as the two previous examiners had found them present in sufficient quantity by the oxydase method to make a diagnosis of lymphatic type. There are fluctuations in blood pictures to be sure, and cases are reported in which one type

has changed to another. The information relative to the latter cases is very meager. Then there is the question of individual observation over which there is no control. It is hoped the evidence submitted will encourage the use of the oxydase method of staining the blood smear to ensure a more accurate distinction between large lymphocytes and myelocytes.

Conclusions. 1. The distinction between lymphocytes and myelocytes by granules in the protoplasm is uncertain by the average examiner with ordinary methods of blood-staining and is liable to render his percentage proportions of these two cells inaccurate. This will result in incorrect type diagnosis of leukemia.

2. The oxydase method of staining the blood smear will be of assistance in making the distinction.

3. A description of a satisfactory method is given.

4. Summarized blood-findings are given which illustrate a possible error in failure to recognize myelocytes by simple method of staining.

I wish to express my thanks to Dr. John Phillips for the opportunity of making examinations of case reported.

THE CURABILITY OF TUBERCULOUS MENINGITIS.

By Francis Harbitz, M.D.,

PROFESSOR OF PATHOLOGY IN THE UNIVERSITY OF CHRISTIANA, NORWAY.

It is now generally accepted that tuberculosis is a curable disease. The struggle against tuberculosis is based in large measure on the fact of its curability, the effort being to secure as favorable circumstances as possible for the infected in order to bring the process to a standstill and cure. Examples of the cure of tuberculosis are numerous even when the very many latent tuberculous foci, particularly in the lungs and lymph nodes, that are cured spontaneously, are disregarded. Thus tuberculosis of lymph nodes in most cases cures itself without giving rise to any clinical phenomena of note, and this occurs in the lymph nodes of the neck, the chest and the abdomen as well as elsewhere. This is also true of tuberculous processes in the skin, mucous membrane, bones and joints. At the postmortem table one may see complete recovery even of the most extensive and destructive forms of tuberculosis of the bones. At the same time such processes may remain latent and encapsulated, but not healed, through years and years, as, for instance, the case of latent tuberculous spondylitis of twenty years' standing that I observed.

The curability of pulmonary tuberculosis is the corner-stone on which rests all our efforts against tuberculosis with the expenditure

of millions for sanatoria and other means to secure recovery in the largest number of cases possible, and in spite of many disappointments there is today no doubt but that sanatoria are of great value both in prolonging life as well as in promoting the definitive cure of tuberculosis in numerous cases, to say nothing about the other important purposes of such institutions. At postmortem examinations there is frequently occasion for wonder at the extent and destruction of tuberculous lesions in the lung that nevertheless have healed; large cavities may form, the walls of which become cleared of caseous masses, and practically complete healing may take place even after years, with extensive scar formation.

Renal tuberculosis is also not incurable as thought at one time. The process may become arrested and encapsulated, with, it is true, practically total destruction of the affected kidney,[1] and sometimes this occurs quietly and in a latent manner. At other times a marked tendency to fibrous arrest and healing of renal tuberculosis is noted, and in a few cases I have observed healing of small local tuberculous processes affecting one or more papillæ with the adjacent lining of the pelvis, and in such cases there no doubt at one time was an active process with excretion of bacilli in the urine. Such a course may explain certain cases of urinary infection with demonstration repeatedly of tubercle bacilli in the urine, in which after renal extirpation it has not been possible to demonstrate any definite tuberculous focus, old or new in the kidney. Assuming that tubercle bacilli were present in the urine, such cases can hardly be explained without there having been present some small focus which has healed completely. While there is no question that renal tuberculosis may heal, this is also true in even greater degree in regard to secondary tuberculous infection of the ureters and bladder—when the passage of tubercle bacilli from the kidneys is stopped the lower localizations may heal rapidly.

Genital tuberculosis also stands in a different light than it did. For some time it has been known that tuberculous salpingitis often heals, whether latent or after having caused definite symptoms, and whether complicated with tuberculous peritonitis or not. Experience has shown that tuberculous epididymitis sometimes lasts for years, and that it even may heal by encapsulation with or without local surgical treatment. On this account radical surgical measures, such as removal of the affected parts, with connected structures, no longer is practised as much as it used to be.

Tuberculosis of serous membrane may heal apparently easily and rapidly. Thus a tuberculous pleuritis may disappear, any grave consequences being usually due to the simultaneous tuberculous process in the lung. That tuberculous peritonitis is curable

[1] Harbitz, F.: Can renal tuberculosis heal spontaneously? Norsk. Mag. F. Lagevivenskaben, 1913, p. 1469.

has been demonstrated, among others, by Winge and Borchgrevink in Norway.

There is, however, one tuberculous localization that still is regarded as hopeless, namely, tuberculous meningitis and tuberculosis in the central nervous system. The usual prognosis in such cases is that tuberculous meningitis results in death in a comparatively short time. The numerous cases in which this disease is the cause of death, especially in childhood, appear to justify this grave outlook. Nevertheless it may be well to review our ideas in regard to this form of tuberculosis. While the physician, as a rule, holds out no hope in this disease—*et immedicable vitium*—there nevertheless are recorded in the literature several observations that indicate the curability of even tuberculosis of the meninges. Thus a number of French physicians, particularly pediatricians, seem to have been early impressed with this possibility. In 1858 Rilliet wrote about the healing of tuberculous meningitis. More recently Barbier and Gougelet[2] discuss this subject, and other observations are being published.

When choroidal tubercles came to be recognized by means of the ophthalmoscope the diagnosis of tuberculous meningitis became more certain. A still better means was furnished by lumbar puncture because it made it possible to demonstrate the presence of tubercle bacilli either directly or by inoculation of guinea-pigs, and after 1891, when this method was introduced, the reports of healed cases of tuberculous meningitis increased rapidly. In 1914 Bokay[3] collected no less than 29 such cases, including 2 of his own, 1 in a boy, aged eleven years and the other in a boy aged two years, in which the diagnosis was established by demonstration of tubercle bacilli in the spinal fluid or by the inoculation of guinea-pigs. If we add 5 older cases in which the diagnosis was made by demonstration of tubercles in the choroid, and if we include certain later cases[4] in which tubercle bacilli were demonstrated, the total number of cases of healed tuberculous meningitis, concerning the diagnosis of which there can be no question, becomes about 40. Then we have further the older, somewhat uncertain cases in which the diagnosis of tuberculous meningitis with recovery was made by experienced clinicians, and finally cases with recovery in which there subsequently developed acute recidivation and death, sometime months and even years afterward.

There would seem to be but little doubt that recovery may succeed tuberculosis of the meninges, but there may be a question whether there was in any of the cases tuberculous inflammation at the base of the brain with partly gelatinous, partly purulent

[2] Sem. méd., 1914.
[3] Jahrbuch. d. Kinderheilk., 1914, 80.
[4] Bacigalupo; München. med. Wchnschr., 1915, Reichmann and Rauch, ibid., 1919.

exudate about the bloodvessels and nerves. In many of the cases with recovery the brain symptoms seem to have been comparatively slight, there being no paralysis of the cranial nerves or other signs of definite localization, and the process of recovery was so rapid that it hardly would be possible for serious defects to heal so smoothly and promptly. It is indeed noteworthy that such acute inflammation may subside so completely and rapidly, and it suggests that possibly meningeal tuberculosis occurs more frequently than suspected, perhaps with evenascent symptoms (meningismus, pseudomeningismus), but this, of course, is merely a hypothesis.

In connection with this matter it may be well to mention the so-called pseudo-tumors described in the literature and which in part are regarded as instances of tuberculous meningitis with recovery; the conditions included under this term are, as a rule, afebrile but with general and local signs of brain tumor, with, however, negative results when postmortem examination is made. In some cases it has been concluded that a tuberculous meningo-encephalitis was present (Oppenheim).

When we come to the anatomic observations that bear on this particular form of tuberculous meningitis, we find that Rilliet in 1853 described a case in a child, aged five and a half years, that was sick for three months with signs of tuberculous meningitis, but recovered; five and a half years later a new attack of meningitis developed with death, and at the postmortem examination there was found, besides the usual lesions of meningitis, firm caseous masses in the depths of a furrow in one of the hemispheres, with thick membranes, and this was interpreted as the remnants of the old "healed" meningitis. Barth[5] reports an instance of tuberculous meningitis in a boy twelve years old who recovered after two weeks. He died twenty-five years later of tuberculosis and there was found a fibrous condition of the leptomeninges with fibrous nodules along the vessels, and these lesions were regarded as the results of the old process. Johann v. Bokai, in 1862, described a meningitis in a girl, aged four years, who recovered, but died three and a third months later of tuberculosis of the lung when there was found small, round, soft, yellow nodules in the meninges over the hemispheres and in the Sylvian fissures. The case reported by v. Leube, in 1889, is well known: recovery from meningitis and death long afterward when small thickenings in the meninges of the upper end of the cord and the medulla with calcified miliary nodules at the base and hyaline degeneration of the vessels. Janssen[6] observed a man, aged nineteen years, who had typical symptoms of tuberculous meningitis but recovered in the course of about six weeks. Some three years afterward he died of pulmonary tuberculosis and in the meninges at the base as well as the convexity were found caseous,

[5] Deutsch. med. Wchnschr., 1894.

[6] Ibid., 1896.

yellowish-white masses and gray as well as yellow tubercles. Brooks and Gibson[7] report the following case: A girl, about four years old, developed what seemed like tuberculous meningitis; tubercle bacilli were found in the spinal fluid; the symptoms, however, subsided gradually, but after about half a year death resulted from a non-tuberculous bronchopneumonia; in the meninges of the brain there was found fibrous changes with scattered fibrous tubercle-like nodules, but no exudate, the ventricles being considerably dilated. Microscopically only fibrous tissue without definite tubercle structure was found. The case is regarded as a tuberculous meningitis undergoing healing. There are a number of other observations, more or less reliable, to the effect that postmortem residues of an earlier tuberculous meningitis were present, but in some cases, though not by any means all, this interpretation is open to doubt. There seems little doubt then but that it is well established, even in the older literature, that tuberculous meningitis may heal with fibrous changes. There are, furthermore, a number of observations indicating that tuberculosis of the meninges may run a chronic course through many months, with peculiar anatomic features indicating a tendency to heal. Thus Busse[8] describes this case: in a woman, aged thirty-seven years, who had presented symptoms of a meningitic nature for about eight months, with emaciation there was found in the pia flat nodules and retracted scars with tubercles and tubercle bacilli, there being much fibrous tissue but no caseation. Busse regarded this as a rare form of chronic tuberculosis with scar formation. Estramann[9] reports the following case: A man, aged thirty-seven years, was sick for at least about a year, the symptoms being headache, vomiting, bilateral hemianopsia, etc. After death there was found an extensive fibrous meningitis at the base with fibrous tubercles without caseation and evidently quite chronic. There were also small calcified nodules in the membranes and an indurated tuberculosis in the lymph nodes as well as a chronic tuberculous skin lesion. The clinical picture resembled somewhat dystrophia adiposa genitalis, but the hypothesis was normal. Rossle[10] describes a chronic tuberculous meningitis in a woman, aged thirty-seven years, sick for seventeen months with marked cerebral symptoms (headache, dizziness, vomiting, spasms, pupillary stasis, and finally chronic convulsions and coma); postmortem there was found at the base of the brain a caseofibrous tissue with conglomerate tubercles in the meninges and the cortex as well as in the choroid plexus, the lateral ventricle being dilated. There was also a chronic tuberculosis of the tracheal lymph nodes. While tubercle bacilli could not be found, which also is true as regards

[7] Lancet, 1912.
[8] Virchows Arch., 1896, p. 145.
[9] Mittheil. a. Grenzgeb. d. Med. u. Chir., xxiii, 191.
[10] Verhandl. d. d. path. Gesellsch., 1914, xvii, 557.

giant cells, the Wassermann reaction was altogether negative, and so Rossle concluded that it concerned a tuberculous process. It is a case of this sort that I wish to report because it bears directly on the question whether meningitis of this kind from time to time may undergo healing.

It concerns a man, aged thirty-two years, under the care of Professor Leegaard. Except for an attack of influenza, in November, 1918, he had been well until in February, 1919. The symptoms of influenza were headache, fever, dizziness, vomiting, etc., and these lasted about one week. The illness in February, 1919, began in about the same way; there was fever, headache, vomiting and hiccough, but these symptoms, except the fever, persisted at the same time as choked disk developed. A little later diplopia, nystagmus, ptosis and facial paresis appeared, with rigidity of the extremities and positive Babinsky. He died July 16, 1919, having been more or less restless and disturbed mentally during the last few days, when ataxia and Romberg's symptom also appeared. After death tubercle bacilli were found in the spinal fluid after much search.

The autopsy showed enlarged lymph nodes in the neck, caseous such as along the trachea and in the hilus of the lungs and along the bronchi, some nodes being sclerotic and calcified. Typical tubercles as well as caseous and hyaline degeneration, together with fibrous changes, were found microscopically.

In the right pleura were a few flat and firm but caseous tubercles and in the lung there were scattered tuberculous infiltrations, with central caseation along the bronchi most marked in the upper lobe and the left apex. The microscope showed tubercles in fibrous transformation.

In the liver, spleen and kidneys nothing special.

The mesentery contained numerous caseous and calcified nodes. There were no tuberculous intestinal ulcers.

The brain was greatly swollen and edematous, with broad gyri and small sulci. On the convexity grayish-white lines paralleled the vessels. Over the entire base the membranes were grayish-white and thick, but without any definite exudate, here and there being scattered small grayish-white, rather firm nodules. In the left Sylvian fossa was a firm, grayish-white nodule as large as a hempseed. On the surface of the cerebellum were flat, very firm nodules. There was a marked internal hydrocephalus, the choroid plexus seemed to be infiltrated and the walls of the ventricles seemed soft and granular, particularly in the fourth ventricle and in the anterior and external parts of the lateral ventricles. No changes in the interior of the brain.

Numerous sections were examined from various parts of the base and elsewhere. There were more or less distinct evidences of a previous tuberculous meningitis and encephalitis with numerous tubercles on the surface of the brain as well as in the interior of the

ventricles. There was no sign of any exudate anywhere, but some infiltration of the membrane with lymphocytes here and there, particularly at the bottom of the sulci and about the larger vessels. However, large stretches of the membranes, particularly over the convexity, were quite free from any infiltration, but tuberculous inflammation had passed into the superficial brain substance along the bloodvessels, causing infiltration of cells in masses as well as bands with formation of small tubercles, consisting almost entirely of epithelial and giant cells, there being only few lymphocytes, and necrosis or caseation was hardly ever seen, but often a fibrous change in concentric order about the tubercles. The tubercles seemed to be chronic, with a definite tendency to heal. The brain substance about the tubercle was affected but very little, being even not markedly edematous; large tubercles of epithelioid cells seemed as is simply pressed into the surface with but little inflammatory reaction in the neighborhood. The walls of the ventricles, however, showed distinct evidences of softening and reaction, there being numerous large tubercles not merely on the surface but also along the vessels and a considerable, sometimes nodular, appendymal proliferation with superficial softening. These changes were more marked in the third ventricle than in the lateral, and the floor of the fourth ventricle contained conglomerate tubercles, with destruction of groups of ganglion cells.

Sections of the spinal cord from the cervical, upper and lower dorsal and lumbar parts showed areas of lymphocytic infiltration in the leptomeninges, with here and there, particularly in the lumbar part, distinct tubercles, consisting mostly of epithelioid cells, situated either in the membrane or extending into the white substance. Some of the bloodvessels in the membrane about the infiltrations were thick and hyaline. There was some infiltration in the spinal nerves. There was also infiltration in the walls of the bloodvessels in the fissures as well as in the small branches that extended into the cord itself; besides infiltrations of lymphoid cells there was also distinct tubercle formation, and tubercles were found about the vessels of the anterior horn and particularly the small branches of the motor ganglion cells. Similar tubercles were found also in Clarke's columns in the posterior horns, and, as stated, in the white substance. There was no edema, no definite degeneration in the ganglion cells and no leukocytic infiltration about these tubercles, which seem to be in the process of healing.

This case is characterized by a certain definite chronicity, shown particularly by the absence of any exudative changes. That the process at one time was exudative is indicated by the presence of scar-like areas in the membranes and thickening with hyalinization of the walls of bloodvessels. It is noteworthy that the tubercles were fibrous and that there was so little reaction about them even when they were situated closely adjacent to large and important

FIG. 1.—Section through Sylvian fissure. Lymphocytic infiltration in the meninges and tubercles in the surface of the brain. At *a* an infiltration of epithelioid cells extending into the brain.

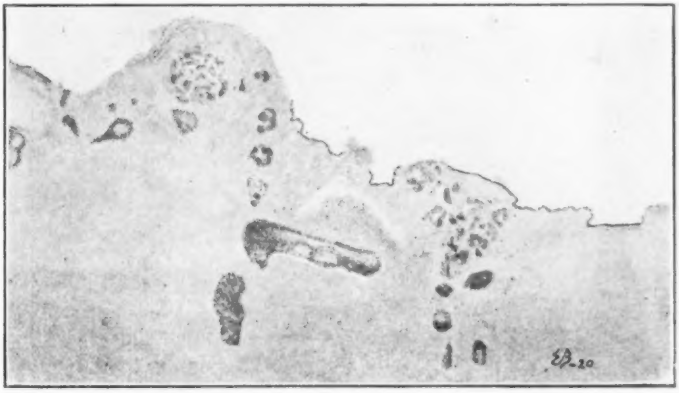


FIG. 2.—Floor of fourth ventricle. Ependyma partly intact, floor nodular, numerous tubercles below the surface especially along vessels.

groups of ganglion cells. Nowhere was there any softening or degeneration of the tubercles. Mention should also be made again

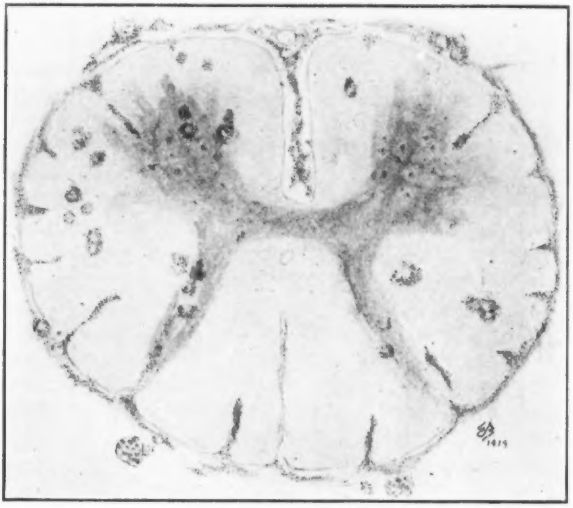


FIG. 3.—Cervical cord. Tubercles in gray and white substance, infiltration of the membrane.

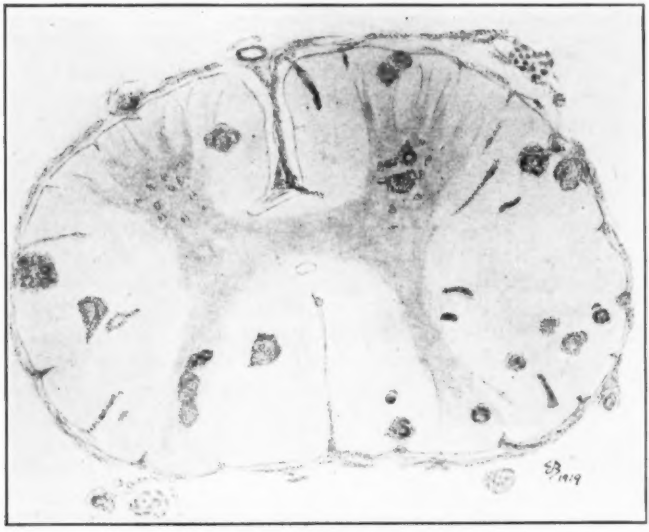


FIG. 4.—Lower part of dorsal cord with numerous tubercles along the vessels.

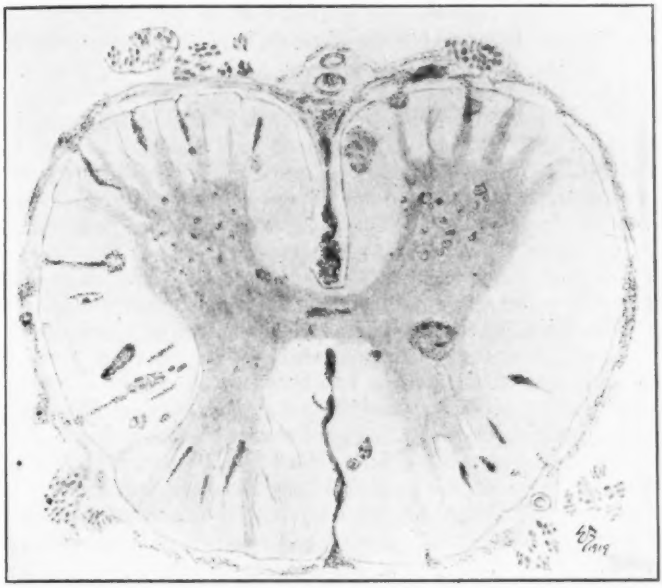


FIG. 5.—The lumbar cord. Infiltrations and tubercles in the membranes, especially in the fissures, as well as along the vessels in the white and gray substance.

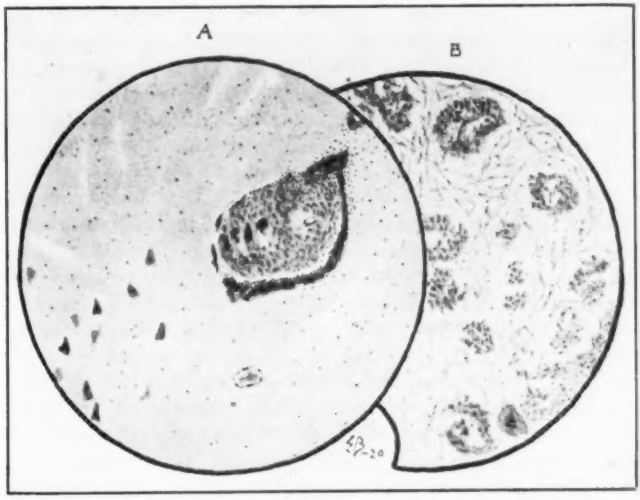


FIG. 6.—*A*, section through anterior horn, showing a large epithelioid tubercle; ganglion cells to the left. *B*, tubercles on the surface of the fourth ventricle, composed of epithelioid cells and free from reactive changes.

groups of ganglion cells. Nowhere was there any softening or degeneration of the tubercles. Mention should also be made again

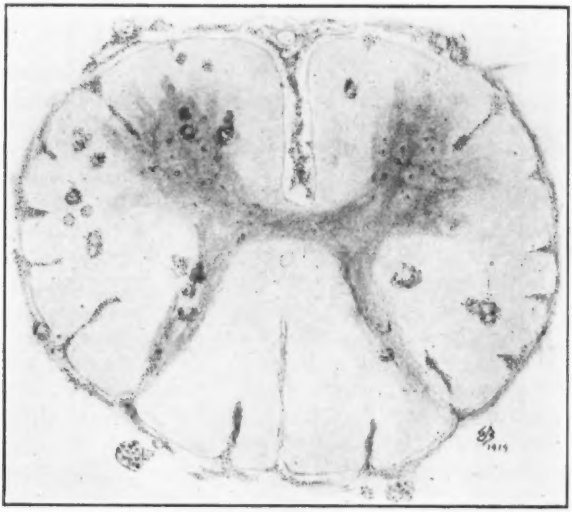


FIG. 3.—Cervical cord. Tubercles in gray and white substance, infiltration of the membrane.

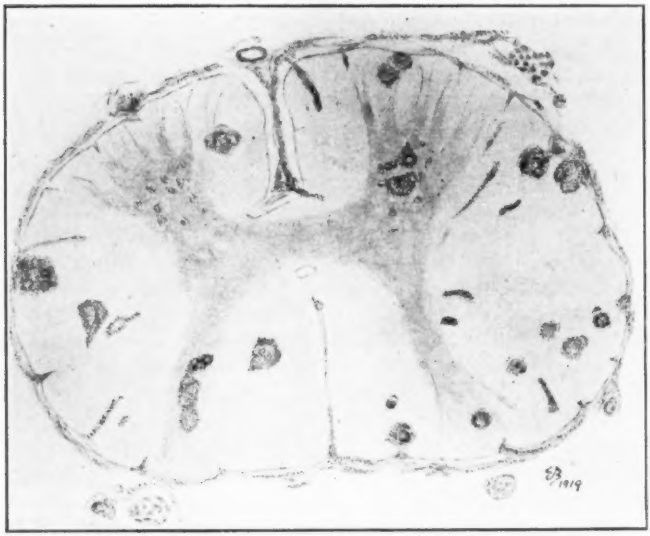


FIG. 4.—Lower part of dorsal cord with numerous tubercles along the vessels.

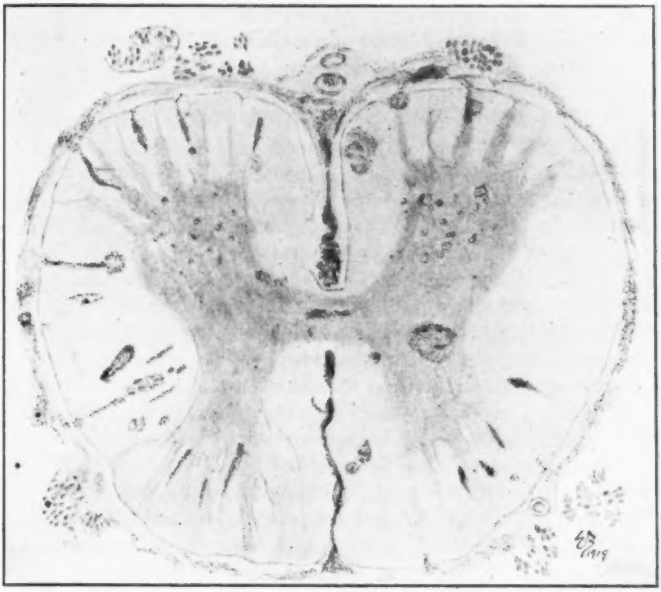


FIG. 5.—The lumbar cord. Infiltrations and tubercles in the membranes, especially in the fissures, as well as along the vessels in the white and gray substance.

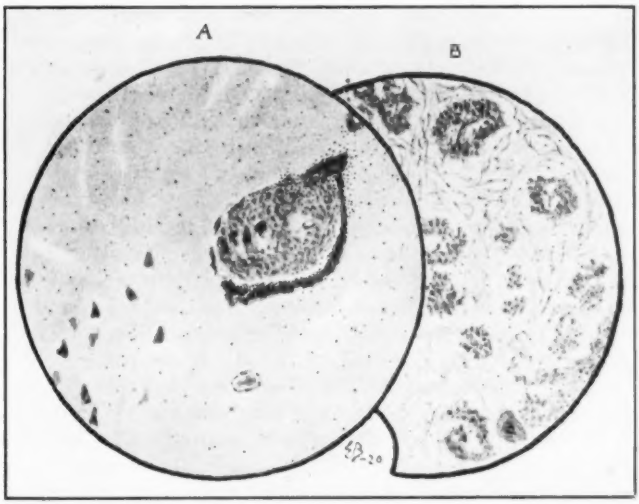


FIG. 6.—*A*, section through anterior horn, showing a large epithelioid tubercle; ganglion cells to the left. *B*, tubercles on the surface of the fourth ventricle, composed of epithelioid cells and free from reactive changes.

of the marked proliferation of glia cells in the wall of the lateral ventricle as an indication of the chronic nature of the process. The case is noteworthy especially on account of the marked tendency of tubercles to develop along the bloodvessels into the substance of the brain and cord, thus giving rise to a condition that may be designated as a tuberculous encephalitis and myelitis as well as poliomyelitis. The poliomyelitic changes were also secondary to the process in the membrane and due to perivascular spread, reminding one of the changes in epidemic poliomyelitis and lethargic encephalitis. In our work on epidemic poliomyelitis Scheel and I[11] advanced the idea that the virus of poliomyelitis infects the leptomeninges first and then the arachnoid fluid, the infection spreading along the vessels, particularly the arteries, and thus reaches the anterior horns in the cord. We pointed out that in tuberculous and other forms of meningitis a similar extension into the substance of the central nervous system may take place, and the case now described lends strong support to the view that infection may reach the substance of the brain and cord in the way indicated. It would seem that in lethargic encephalitis also extension may take place in this way.

Cases like the one described would seem to be rather infrequent, particularly such marked degree, but less marked examples of tubercle conglomeration over limited areas of the brain surface, without diffuse meningitis, and even with focal symptoms, are probably not so rare. I observed a case of this kind in a man, aged thirty years, who had been sick for about four months with paresis in the left arm; there were signs of tuberculous meningitis here and there, most over the right convexity, and then large conglomerate tuberculous masses in and about the right sulcus centralis, the process being of a chronic nature with tendency to heal.

From the results of the observations at hand it may be concluded that tuberculous meningitis may heal, and even in cases in which rather extensive lesions with exudate and tubercle formation have developed. What may be the reason that tuberculous meningitis occasionally takes this course? It may depend on the nature of the infection, and it seems that this curable form of meningitis has occurred largely in persons who have suffered from chronic and relatively benign forms of tuberculosis. It is probable, however, that a more important factor is increased resistance on part of the body, which bears some relation to the age of the patient. It is interesting to note that while about 60 per cent. of all cases of tuberculous meningitis occurs in the first two years in life and quite regularly result in death, the cases with recovery have occurred in older children and in adults. Bokai found that in 18 such cases the age ran from two to twelve years and in 12 cases from sixteen

[11] Pathologisch-Anatomische Untersuchungen über Poliomyelitis und verwandte Krankheiten, Videnskapsselsk's Skr. 1 Math. Naturv. Klasse, 1907, nr. 5.

to forty-four, and in the recently observed cases it concerned adults. Consequently it would seem that an increased resistance must be of considerable importance.

With reference to the prognosis, it may be noted that while epidemic meningitis frequently terminates in a chronic condition with internal hydrocephalus and other serious changes, tuberculous meningitis, even when extensive lesions have formed, may heal without any serious defects. In the case now reported there was an internal hydrocephalus in the early stages.

CLASSIFICATION OF GOITER: AN ANALYSIS OF ONE HUNDRED CASES.[1]

By Carrington Williams, M.D.,
Assistant Surgeon, St. Luke's Hospital, Richmond, Va.

The classification and nomenclature of goiter have always been unsatisfactory, for the reason that in spite of the large number of cases operated on and the extensive material for pathologic examination no standardization of title has resulted.

It is generally agreed there are two great classes of goiters: The simple goiter, without symptoms other than pressure, and the toxic goiter, with symptoms referable to various organs other than the thyroid gland.

Plummer[2] and Wilson,[3] since 1914, have written regarding the clinical and pathologic difference in cases of toxic goiter, but there is little evidence in the literature that their views have been accepted. Plummer, in a paper from the Mayo Clinic, read in June, 1919, divided the toxic type of goiter into two groups, one of which he called hyperthyroidism and the other exophthalmic goiter. Our experience with goiter is in accordance with this division. Our series of cases is not sufficiently large to prove the points to be made nor is there sufficient accuracy or detailed clinical data to be certain of the proper classification of borderline cases; but we wish to record our experience in line with the above writings.

Simpson,[4] in a recent article, has classified goiter from pathologic specimens sent to him for diagnosis, and his conclusions are largely in accord with our own observations.

We wish to present the last 100 cases of goiter operated on in St. Luke's Hospital during the period of eighteen months. All

[1] Read before the Richmond Academy of Medicine and Surgery, June 22, 1920.
[2] Keen's Surgery, vol. vi; Am. Jour. Med. Sc., December, 1913; Collected Papers of the Mayo Clinic, 1914 to 1918.
[3] Journal-Lancet, xxiv, 4.
[4] Surg., Gyn. and Obst., February, 1919.

cases admitted to the surgical service were operated on except 3. One of these was a woman, aged fifty-five years, with extensive myocardial and renal degeneration, who was treated by the roentgen-ray and has since died. The second was a man, aged forty-five years, with thyroiditis following influenza and associated with chronic and severe myocarditis and aortitis. The third was a woman, aged forty-seven years, with a large, very hard goiter and bony metastasis in the lumbar spine. The diagnosis of carcinoma of the thyroid with spinal metastasis was made and she was considered hopeless. These 3 cases are not included in this series. It should be noted here that cancer of the thyroid will occur in about 1 per cent of all goiters and should be considered when dealing with this condition.

We have divided our cases into three groups:

Group I contains the simple goiter, about which there is little to be said. They have few symptoms occasionally complaining of pressure, as evidenced by hoarseness, obstruction to breathing and difficult swallowing. They come to operation for relief of these symptoms, or as is more frequent, for a correction of the deformity.

A summary of the cases in this group is as follows:

Number, 61.

Sex: Males, 4; females, 57.

Age: Twelve to sixty years. Average, thirty-two and a half years.

Duration: Two months to twenty-five years. Average, seven and a half years.

Growth: Gradual increase in size in all cases except 3, these of twenty-five, ten and five years' duration had grown more rapidly in the year preceding operation. The pathologic report in all 3 cases was cystic colloid goiter.

Tachycardia: One case.

Tremor: The fine fibrillary tremor was absent in all cases. A few had a gross tremor. Loss of weight was noted in only 2 cases.

Nervousness: Thirty-six per cent. of the cases were nervous but none were of the toxic type of nervousness.

Recurrence: Two cases were recurrent. The pathologic reports were cystic and cystic colloid goiter.

PATHOLOGIC REPORT.

Simple adenoma	12
Colloid goiter	24
Cystic goiter	10
Fetal adenoma	10
Hematoma	1
Colloid with parenchymatous hyperplasia	1
Adenoma with parenchymatous hyperplasia	1
No report	2
Total	61

In this group it should be noted that 2 cases were recurrent, both of cystic type. One case was a hematoma of seven years' standing, resulting from a severe strain in a wrestling match; the patient was a powerfully built young man. Two cases showed parenchymatous hyperplasia in addition to colloid and adenomatous goiter, and though clinically in this group, must be considered as borderline cases with Group II. Both of these cases had goiter of short duration, and without surgical intervention would have developed hyperthyroidism and have been definitely in Group II.

To avoid confusion the pathology of goiter, with special reference to our classification, should be mentioned. The simple adenoma is comparable to the adenoma found in other glands. The colloid goiter is composed of multiple dilated tubules filled with colloid material. The fetal adenoma is composed of alveoli lined with a single layer of cells embedded in hyaline material.

The toxic goiter cases we formerly considered as varying degrees of the same pathologic process, but in the light of Plummer's papers and our own observations we would divide them into two groups, with rather decided clinical contrast.

Group II we call hyperthyroidism, as will be described later.

Group III we call exophthalmic goiter.

Group II presents a very interesting picture. The patients are middle age and have had a goiter for a long time without symptoms. These quiescent goiters suddenly begin to grow, and coincident with the growth the patients become restless and nervous; they have attacks of palpitation, the heart-rate becomes accelerated and they lose weight, but they do not have the fine tremor of the third group nor do they have the exophthalmos. One case in this group had the toxic symptoms for two years, but there was no exophthalmos; all cases in Group III of that duration had the typical exophthalmos. Experimentally this group can be reproduced by feeding thyroid extract, and they promptly recover when the feeding is stopped.

A summary of the cases in this group is as follows:

Number: 20.

Sex: Male, 1; females, 19.

Age: Thirty-four to fifty-eight years. Average, forty-seven years.

Duration: Two months to thirty years. Average, eleven years.

Growth: Recent growth of goiter in 10 of 14 cases recorded, 77 per cent.

Tachycardia: Present in 35 per cent.

Exophthalmos: Absent in all cases.

Tremor: The fine fibrillary tremor was absent in all cases. Gross tremor in 35 per cent.

Loss of Weight: 5 to 100 pounds in 40 per cent.

Nervousness: All these patients complained of being nervous. In one case, the only postoperative death, it amounted to a dementia.

PATHOLOGIC REPORT.

Colloid with parenchymatous hyperplasia	7
Fetal adenoma	3
Colloid	6
Simple adenoma	1
Cystic	1
Fetal adenoma with parenchymatous hyperplasia	1
No report	1
Total	20

The patients in Group II have for years had the pathology described for Group I. They still have this pathology, but some of the tubules have papillary projections into the lumina from cellular proliferation, and, besides, there are a few areas of closely packed tubules containing little or no colloid material.

Group III embraces the patients with the classic symptoms of exophthalmic goiter; they present a line of symptoms including all in Group II, but in addition definite points which put them in a separate class. We will not attempt to go into theories of the cause or even the pathology of exophthalmic goiter outside of the thyroid gland. These patients have small goiters; they have had symptoms for a relatively short while and the onset of the toxic symptoms is coincident with or previous to the appearance of the goiter. Two of these cases were clinically put into this group, but the pathologic report corresponds to the picture to be expected in Group II. It is interesting to note that one of these two was a borderline case and had no exophthalmos, while the other is a frank exophthalmic which we consider as developing independently rather than on the existing adenoma. Exophthalmos has been considered as a symptom frequently absent in Graves's disease; of these cases 60 per cent. have exophthalmos, while in the 6 cases without it 5 were of one year or less duration and the sixth was a doubtful Group III. Practically all of the cases have tremor, tachycardia and the typical nervousness. The tremor in these cases is the fine fibrillary motion of the fingers quite distinct from the gross tremor seen in Group II. The tachycardia is much more pronounced in this than in the preceding group.

A summary of the cases in this group is as follows:

Number, 19.

Sex: All females.

Age: Fifteen to fifty-one years. Average, thirty-three.

Duration: Two months to seven years. Average, two years.

Growth: Recent growth of goiter in 8 of 14 cases recorded, 57 per cent.

Tachycardia: Present in 86 per cent.

Exophthalmos: Present in 60 per cent.

Tremor: The fine fibrillary tremor present in 86 per cent.

Loss of Weight: Ten to forty pounds in 30 per cent.

Nervous: All were typically nervous, as evidenced by rapid speech, movement of limbs, excitability, etc.

PATHOLOGIC REPORT.

Severe papillary hyperplastic parenchymatous	14
Simple adenoma with parenchymatous hyperplasia	1
Colloid with parenchymatous hyperplasia	1
No report	3
Total	19

The pathology typical of Group III is the hyperplastic parenchymatous goiter, which is composed of closely packed tubules lined with multiple rows of large cells with little or no colloid material.

We will dismiss the case in Group I, the simple goiter with the brief discussion already given. We believe, however, that the demonstration of hyperthyroidism developing in the simple goiter will give additional importance to the removal of this quiescent but potentially dangerous pathology.

It has been our custom until recently to classify all the other cases with toxic symptoms as varying degrees of the same process, and although we have used a variety of terms we have meant the same disease, and, as a rule, have simply called it hyperthyroidism. We now believe, however, that there are two very definite groups of these cases and propose to call one, Group II, hyperthyroidism to signify that the cause of the toxemia is an increased secretion and absorption of the thyroid secretion. In Group III we adhere to the time-honored title exophthalmic goiter, because we have no better name. We feel that this condition is a clinical entity, and although we want to avoid the mooted questions of pathology and etiology, we believe neither is limited to the thyroid gland.

The clinical grounds for this grouping we believe to be sufficient. The patients in Group II are older women, forty-seven years of age against thirty-three in Group III. They have had the goiter for a number of years, eleven as opposed to two. The goiter has given no symptoms for long periods; the toxemia has been present from six months to two years, and is coincident with the recent growth of the gland, while the exophthalmic, or Group III, has had the symptoms as long as the goiter, and in some cases even without apparent enlargement of the gland. Perhaps the most striking difference in symptomatology is the exophthalmos; it is absent in all cases in Group II but present in 60 per cent. of Group III, being absent only in early cases or in cases doubtfully classified. We believe that cases in Group II will never develop exophthalmos while all cases in Group III will have it if of long enough duration. A larger percentage of cases in Group III have tachycardia, 86 per cent. against 35 per cent. in Group II, but no other practical difference was noted in this symptom. The tremor in the two groups bears the same percentage ratio as tachycardia, but the tremor of the exophthalmic is more definitely beyond the patient's control and more rapid with shorter excursions than that of the hyperthyroid.

Pathologically the grouping is quite interesting. The tissue was examined by Dr. Hopkins, and in his absence by Dr. Budd, quite independently of any clinical data, and although the reports are by no means positive proof of our position, we feel that for routine examination they are confirmatory, and with more detailed study we believe they will tally more exactly. In Group II all cases originally had a goiter of simple type; 40 per cent. of these goiters showed an active hyperplasia in addition to the old goiter, 15 per cent. were fetal adenomata and 40 per cent. showed only the simple type of goiter.

In some of these last cases the same slide would show an old pressure atrophy and a recent hyperplasia of the cellular elements, which has been described fully by Wilson.

In Group III only two specimens, 10 per cent., showed goiter of simple type with hyperplasia of the cellular elements, and of these one was doubtfully classified. Fourteen, 74 per cent., showed the typical papillary hyperplasia of the parenchyma.

Conclusions. Toxic goiters should be regarded as belonging in two definite groups, first, those in whom the intoxication is due to a recent proliferation of parenchyma in an old goiter, our Group II, and second those in which the thyroid hyperplasia is primary and probably associated with other pathology, our Group III.

The simple goiter, Group I, should be surgically removed not only for relief of pressure and for cosmetic improvement, but also to remove the danger of hyperthyroidism and cancer which may develop as the patient and the goiter become older.

The patients in Group II can be relieved by removing the goiter; they may expect perfect recovery unless the operation is delayed until thyroid stimulation has seriously damaged other vital organs. They will become progressively worse if not treated, but will not develop into Group III, the exophthalmic goiter.

Group III cases are improved by surgical treatment; the prognosis, however, is not comparable to what may be expected in Group II. We believe that the best results claimed in treating exophthalmic goiter have been due to operations on cases in Group II which is not exophthalmic goiter. The converse, however, is true—that is, that the poor results are in cases which we would classify in Group III. In spite of this, however, we believe that surgery is the best treatment now known for exophthalmic goiter.

The roentgen-ray and radium treatment of goiter should be confined to cases in Group III, and it is possible that with further development the radiologist may be able to take precedence over the surgeon in Group III cases.

I wish to acknowledge my indebtedness to Dr. Stuart McGuire, on whose service these cases were operated, and to Dr. E. G. Hopkins, who examined the pathologic specimens.

MULTIPLE FLUID COLLECTIONS IN THE CHEST IN THE COURSE OF THERAPEUTIC PNEUMOTHORAX.[1]

By Barnett P. Stivelman, M.D.,

and

Joseph Rosenblatt, M.D.,

Bedford Hills, N. Y.

It is the purpose of this paper to call attention to multiple fluid collections in the chest that occur in the course of induced pneumothorax. This condition cannot be detected by physical examination, and it is recognized only by the characteristic multiple fluid-levels shown on roentgenologic examination. There is usually seen one or more secondary fluid-levels superimposed upon and parallel to the level of the main effusion, and under the fluoroscope a fluid wave can be elicited on each level independently. Among 32 cases of hydropneumothorax we encountered this condition in 5 instances.

It is obvious that the essential factor entering into the causation of such multiple fluid collection is extensive pleuritic adhesions, but the exact mechanism of their production requires further explanation. It would be reasonable to assume that this condition is due to adhesions so distributed as to divide the potential pleural cavity into two or more non-communicating compartments, so that when attempts to induce pneumothorax are made at different points of the chest, two or more pneumothorax pockets may be produced, and when an effusion subsequently supervenes the fluid accumulates in each compartment separately, or pneumothorax is induced in one compartment and a spontaneous pneumothorax occurs in a compartment adjacent thereto.

But while the just described mechanism explains the causation of multiple localized hydropneumothoraces in one of our cases it does not do so in the others that came under our observation, inasmuch as we succeeded in inducing a fair pneumothorax in these cases at the first attempt, and all subsequent punctures were made in areas where the fluoroscope showed a definite pneumothorax, thereby excluding the possibility of the existence of independent pockets.

In view of frequent roentgenologic examinations, before and after the development of the effusions, we are led to believe that in most cases this condition is due to sheet-like adhesions spreading in hammock-like fashion from the visceral pleura across the pneumothorax area to the chest wall. These adhesions, when an effusion supervenes, serve as a receptacle to catch the fluid secreted from the pleural surface above their insertion, and at the same time part

[1] From the Montefiore Home Country Sanatorium, Bedford Hills, N. Y.

of the main effusion below may also be entrapped therein by change of the patient's posture.

It is pertinent to interpolate that certain multiple fluid collections are due to fluid-containing cavities coexisting with hydropneumothorax.

Report of Cases.

Multiple fluid collections due to a spontaneous pneumothorax superimposed upon a limited induced pneumothorax.

Case I.—A. C., aged twenty years, admitted August 12, 1918, with a typical history of active pulmonary tuberculosis and recurrent attacks of pleurisy on the right side. Examination showed extensive, active tuberculosis on the right side. Right pneumothorax was induced on December 2, 1918. Fluoroscopic examination after the first few inflations showed a fair collapse of the right upper lobe; the lower lobe was held down by adhesions. On January 19, 1919, the patient developed chills and fever and hydropneumothorax was detected two days later.

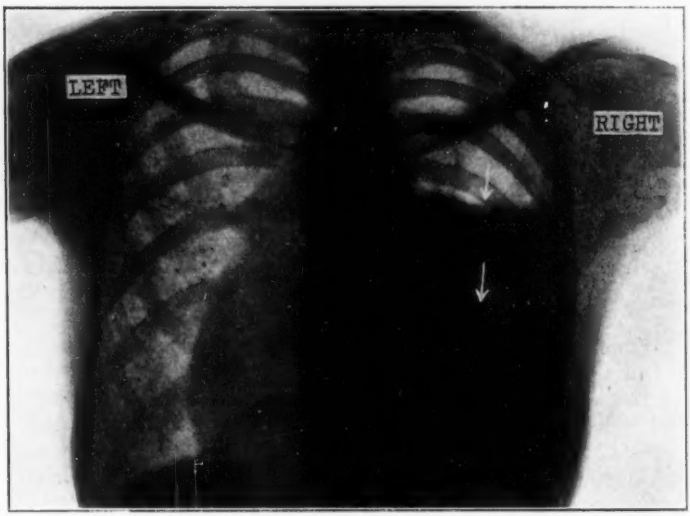


Fig. 1.—Case A. C. Note two fluid levels on right side.

Physical examination subsequently showed the fluid to be up to the third rib, breath sounds and whispered voice being practically inaudible below that level.

On January 22 the patient was seized with a severe stabbing pain in the right lower midaxillary region, and when she was first seen

she was dyspneic and quite cyanosed. Physical exploration of the chest revealed amphoric whisper and distant amphoric breathing below the described level. The possibility of a spontaneous pneumothorax was suggested, inasmuch as previous fluoroscopic examinations showed that the lower lobe was not at all collapsed. On January 28 fluoroscopic examination disclosed two definite fluid levels, each giving an independent splash. The two pockets seemed to be non-communicating. A roentgenogram (Fig. 1) taken the same day confirmed the fluoroscopic findings.

It is evident that in this case the two fluid levels were caused by two independent pockets of hydropneumothorax, one artificial and one spontaneous.

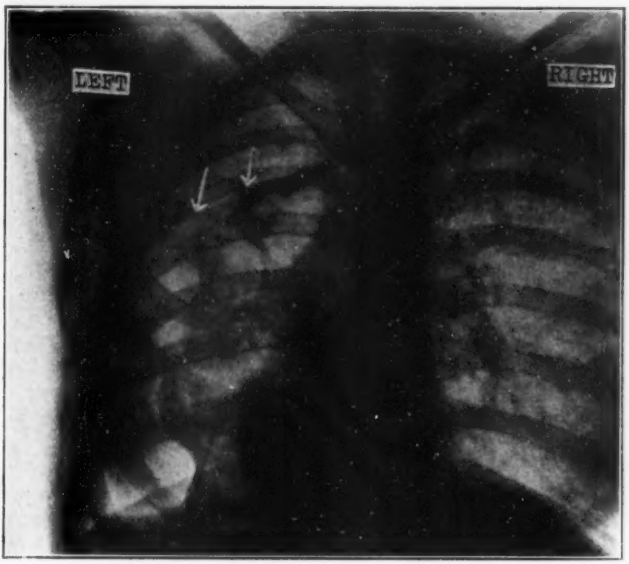


FIG. 2.—Case M. L. Note adhesions on level of second and third ribs.

MULTIPLE FLUID COLLECTIONS CAUSED BY HAMMOCK-LIKE ADHESIONS.

CASE II.—M. L., aged twenty-five years, housewife, admitted March 10, 1919, with extensive and active left-sided tuberculosis. Left pneumothorax was induced July 30, 1919. A roentgenogram taken October 21, 1919 (Fig. 2), shows a fairly complete collapse of the left lung except that there are bands of adhesions stretched across the pneumothorax area to the chest wall on the level of the second and third ribs. During November, 1919, the patient developed an effusion, and a roentgenogram (Fig. 3) taken December 19,

1919, shows a hydropneumothorax with two definite fluid levels, one on the level of the second rib and one on the level of the fifth rib.

It is evident that in this case the upper compartment of fluid collected on top of adhesions that have been present prior to the induction of pneumothorax, inasmuch as the upper fluid level corresponds exactly to the level of the adhesions that were definitely seen before the effusion developed.

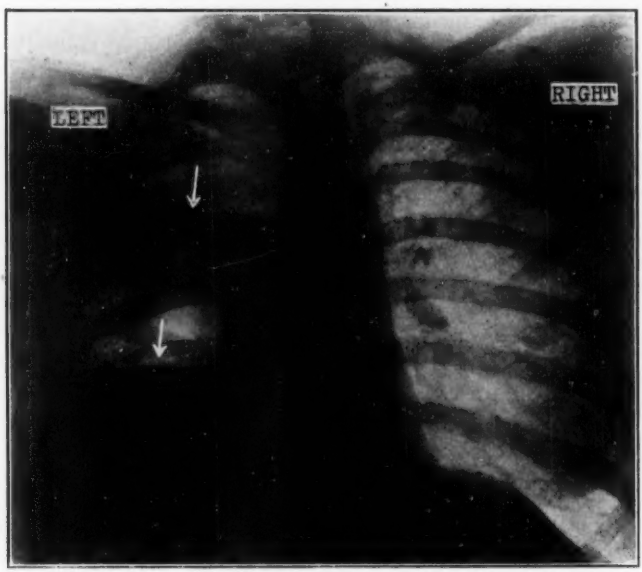


FIG. 3.—Case M. L. Note fluid levels on left. The upper level corresponding to location of adhesions as seen in Fig. 2.

HAMMOCK-LIKE ADHESIONS AS A RESULT OF PREËXISTING THICKENED INTERLOBAR SEPTUM PRODUCING MULTIPLE FLUID LEVELS.

Sheet-like adhesions are sometimes the result of pathologic changes in the interlobar septum. When pneumothorax is induced in these cases the parietal and visceral pleuræ remain adherent at a point corresponding to the interlobar septum, and the lung may be collapsed above and below that level, thus leaving a shelf-like sheet of fibrous structure on which fluid may accumulate. The following case illustrates this condition:

CASE III.—M. P., aged twenty-two years, admitted July 19, 1919, with a typical history of pulmonary tuberculosis. Examination showed tuberculous involvement of the right upper and middle lobes and left apex. A roentgenogram (Fig. 4) showed diffuse infiltration throughout the upper two-thirds of the right lung, with

multiple small cavities in the infraclavicular region. At the level of the third rib anteriorly there was a small, very dense, triangular

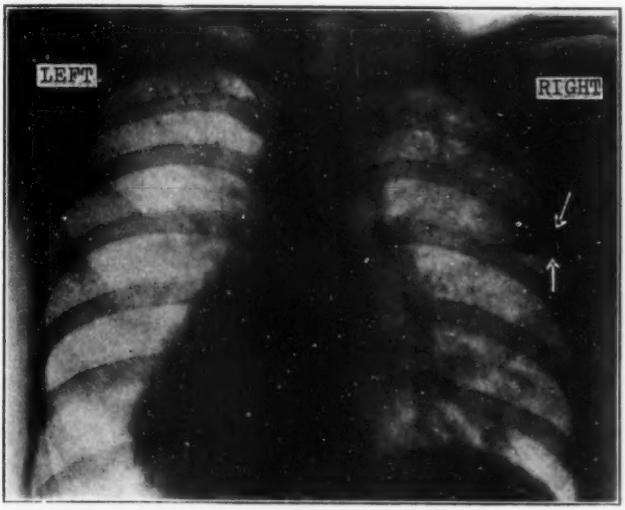


FIG. 4.—Case M. P. Note density in region of interlobar septum on right.

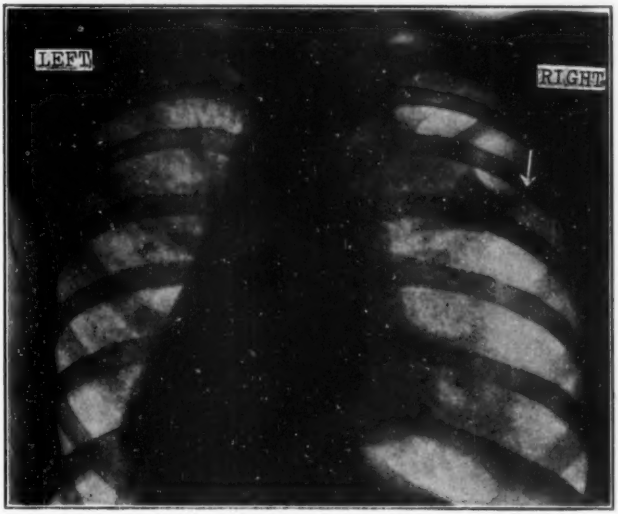


FIG. 5.—Case M. P. Note adhesions in location corresponding to location of thickened interlobar septum seen in Fig. 4.

area, the base of the triangle being toward the periphery. This was undoubtedly a thickened interlobar septum.

A right pneumothorax was induced on August 8, 1919, and a roentgenogram (Fig. 5) taken six weeks later showed an irregular area of pneumothorax occupying the major part of the right pleural cavity, and there was a heavy band of adhesions running horizontally from the lung to the chest wall on the level of the third rib. This point corresponded exactly to the location of the thickened interlobar septum seen on a previous plate. During November, 1919, the patient developed an effusion, and a roentgenogram (Fig. 6) taken November 25, 1919, showed three fluid levels, the

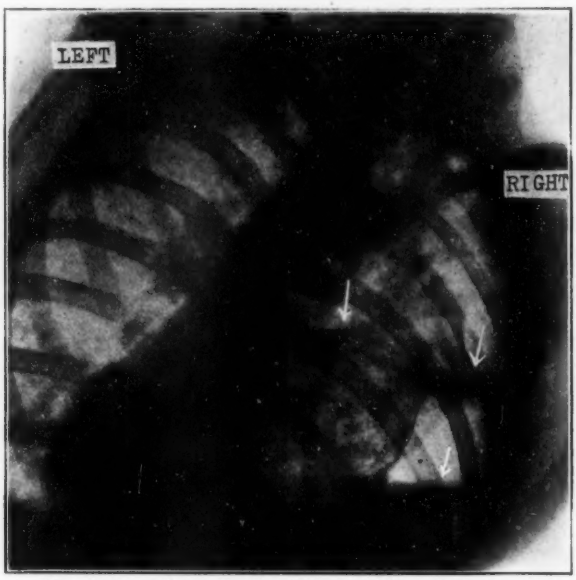


FIG. 6.—Case M. P. Plate taken in oblique position. Note three fluid levels. The uppermost probably due to a fluid-containing cavity. Middle level in location of thickened interlobar septum seen in Figs. 4 and 5.

main fluid level at about the fourth rib, a secondary fluid level at the third rib and a small fluid collection at the third space near the root, each fluid level giving an independent fluid wave on fluoroscopy.

In this case it is obvious that the hammock-like adhesion on which the secondary fluid collection accumulated is due to preexisting pathologic changes in the interlobar septum, as a comparison of Figs. 4, 5 and 6 will readily show. The small fluid collection at the third space near the root is most probably due to a cavity partly filled with fluid.

MULTIPLE FLUID LEVELS CAUSED BY SHELF-LIKE ADHESIONS FORMED BY THE ORGANIZATION OF THE EXUDATE PRESENT.

In the above-described cases the adhesions that caused the secondary pockets of fluid were present prior to the induction of the pneumothorax, but we also observed cases in which there were no preëxisting adhesions in the pneumothorax area; but as a result of the organization of part of the exudate, shelf-like septa were formed. These newly formed fibrous structures supported part of the fluid, and on roentgenologic examination multiple fluid levels were seen. The following cases illustrate this condition:

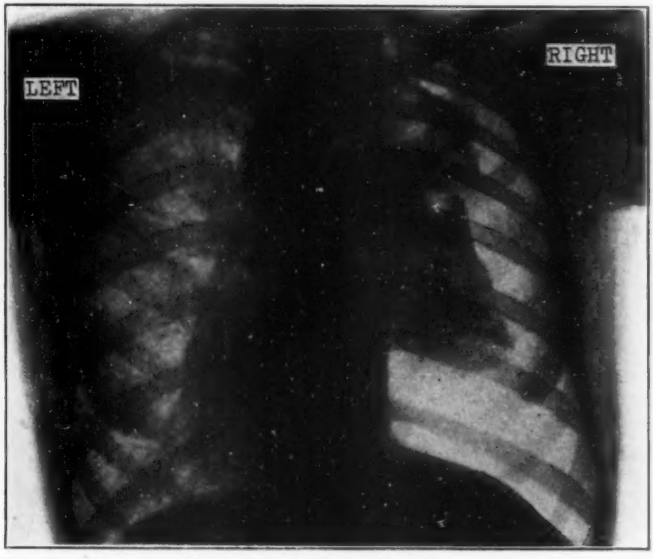


FIG. 7.—Case G. F. Note small adhesions at level of second space and absence of adhesions below.

CASE IV.—G. F., female, aged twenty-six years, housewife, was admitted May 5, 1919, with extensive, active tuberculosis involving the entire right lung and the left apex. Right pneumothorax was induced June 19, 1919, and a roentgenogram (Fig. 7) taken June 24, 1919, shows a fairly complete collapse of the entire right lung. The collapse was specially marked at the base, the lung being collapsed upward and inward. There was, however, a band of adhesions at the level of the second space running from the lung to the chest wall.

During the month of September, 1919, the patient developed an effusion, and a roentgenogram (Fig. 8) taken September 24, 1919, showed three levels of fluid at the levels of the second, fifth and

sixth ribs respectively. Fluoroscopy showed independent fluid waves on each fluid level.

In this case, besides the fluid collection in the region of the pre-existing adhesions at the second space, there is another secondary fluid level at the fifth rib, where, as seen from the previous plate, there were no adhesions. It is certain, therefore, that the adhesions causing this secondary fluid-level were newly formed as a result of the organization of the exudate.

Case V.—R. P., male, aged forty-eight years, tailor, was admitted January 14, 1918, with extensive tuberculosis involving the entire left lung. Left pneumothorax was induced May 13, 1918.

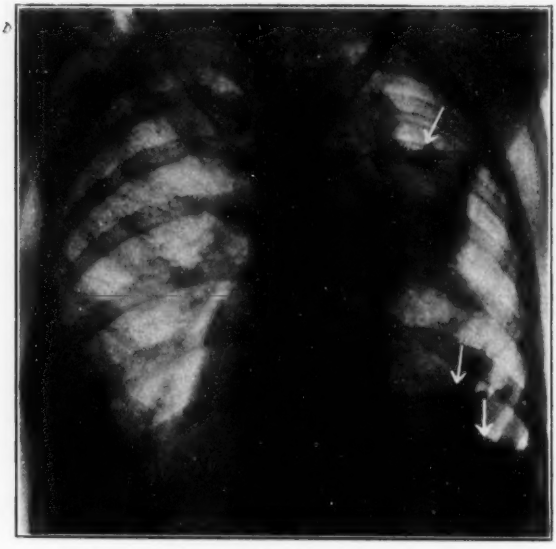


Fig. 8.—Case G. F. Note three fluid levels. The uppermost in region of previous adhesions. The middle in an area previously free from adhesions.

Fluoroscopy, after the first few inflations, showed a localized pneumothorax occupying the axillary portion of the lower half of the pleural cavity.

During December, 1918, the patient developed an effusion and a roentgenogram taken January 7, 1919 (Fig. 9), showed three fluid-levels within the area previously occupied by free pneumothorax, the relation of the three fluid-levels to each other being somewhat step-like in character. Under the fluoroscope three independent fluid waves were seen.

Here, again, the triple fluid-levels developed in an area previously

free from adhesions, so that the organization of the exudate was undoubtedly the cause of the secondary collections of fluid.

Summary. 1. Careful observation of 32 cases of hydropneumothorax disclosed the presence of multiple fluid collections in 5 cases.

2. This condition could not be detected without the aid of the roentgen ray, which showed characteristic multiple fluid-levels.

3. Two or more independent hydropneumothorax pockets may be produced as a result of attempts to induce pneumothorax at different levels of the chest or a localized spontaneous pneumothorax may occur adjacent to a pocket of artificial hydropneumothorax.

FIG. 9.—Case R. P. Note three fluid levels on left side.

4. The most important factor in the causation of this condition is pleuritic adhesions which spread out in hammock-like fashion from the visceral pleura across the pneumothorax area to the chest wall. These adhesions may be present before the induction of the pneumothorax and may occasionally be the result of a thickened interlobar septum, or they may be newly formed as a result of organization of the exudate.

5. The coexistence of a fluid-containing cavity with a hydropneumothorax may also give rise to multiple fluid levels.

NEPHROLITHOTOMY IN HORSESHOE KIDNEY.

By K. P. A. Taylor, M.D.,

SURGICAL SERVICE OF JOHN B. DEAVER, M.D., UNIVERSITY OF PENNSYLVANIA HOSPITAL, PHILADELPHIA.

The occurrence of pathology associated with a horseshoe kidney is sufficiently rare to warrant report.

The horseshoe kidney is one variety of the congenital anomalies met with in the kidney. During the entrance of the fetal kidneys into the abdominal cavity and their ascent to the normal position it is thought that occasionally they are caught in the ring formed by the umbilical arteries (Lewis and Papez). During this arrest in movement, fusion of the two kidneys is thought to take place.

Fusion may occur in any manner. One kidney may be superimposed upon the other ("disk kidney") or the upper pole of one kidney may become fused with the lower pole of the other ("sigmoid kidney"). More frequently, however, fusion is between the two upper or the two lower poles, the lower poles being most commonly united.

The isthmus connecting the two poles is of mesoblastic or parenchymatous tissue and varies in thickness from a few centimeters to the normal thickness of the kidneys.[1] The concavity is usually down and the greater the thickness of the isthmus the more caudal is the kidney.

The pelves and ureters are usually ventral to the kidney. The pelves are frequently anomalous in containing two rows of calices (dorsal and ventral) and no major calix. The blood supply is almost always anomalous. Renal arteries may be found in numbers of six or more, passing to each kidney proper, with corresponding veins.

Occurrence. Roth[2] found five horseshoe kidneys in 1630 autopsies. The Berlin Pathological Institute reported six in 6200 autopsies. Statistics of Guy's and the London Hospital together with those of Victoria Hospital show 16 horseshoe kidneys in 13,505 autopsies.[3] The average incidence from these and other figures is 0.7 per cent. The incidence in males has been found to be much higher than that in females, some reports estimating it at 14 to 1.

Pathology. Horseshoe kidney is encountered relatively more frequently in the operating room than at autopsy. This fact is taken to indicate that the horseshoe kidney, by reason of its low position and the twist in the renal pelves to attain their ventral position, is predisposed to pathology. The most common lesions

[1] Lipschutz and Hoffman: Ann. Surg., 1918, lxviii, 39.
[2] Veroeffentlichungen d. Hufelandischen Gesellschaft, 1910.
[3] Oehler: Beitr. z. klin. Chir., 1914, lxxxix, 223.

are hydro- and pyonephrosis.[4] Braasch[5] reporting the horseshoe kidneys which came to operation at the Mayo Clinic, found hydronephrosis in 4, sarcoma in 1 and essential hematuria in 1, while 4 were without gross pathology and were met with accidentally.

Diagnosis. The diagnosis is occasionally made by inference. If both kidneys are palpated in a distinctly caudal position, and particularly if their lower poles are felt to incline toward the midline, the diagnosis should be entertained. The entire horseshoe mass may be palpated occasionally. Israel[6] and Newman[7] have been able to do so in single cases. The pyelogram may show the pelves lower than normal and distended. Frequently the contrast fluid will run out of the pelves as soon as it is put in because of their vertical position.[8] If a stone is present the shadow may be lower than normal, as opposite the second or third transverse lumbar processes.[9]

Literature. Most of the operations upon horseshoe kidney have been directed against a pyo- or hydronephrosis. Exposure and mobilization and control of hemorrhage are the main difficulties.

Zondek,[10] Rovsing,[11] Oehler,[12] Socin,[13] and the Mayos[14] have successfully removed part of the distended pelvis. Operations for stone have been less frequent. Rovsing[15] reviews 4 cases of horseshoe kidney. In one of these an attempt was made to remove a stone without success. After operating through the lumbar incision in his first 2 cases Rovsing strongly advised the transperitoneal route. In 2 cases Rovsing divided the isthmus and in 1 case obtained complete relief from pain, referred from one side of the back to the other, which he considers characteristic of horseshoe kidney *per se*.

Rumpell[16] successfully removed a stone which cast a shadow opposite the second and third lumbar vertebræ. There was an associated pyonephrosis. The lumbar incision was used. In this case collargol instilled into the kidney pelves ran out as soon as it was put in.

Lange[17] successfully removed a stone through the lumbar incision. No pyelogram was made.

[4] Tr. Am. Assn. Gen.-Urin. Surg., 1913, viii, 289.
[5] Lipschutz and Hoffman: Ann. Surg., 1918, lxviii, 39.
[6] Chirurg. klin. der Nierenkrankheiten, Berlin, 1901.
[7] Lancet, 1917, ii, 236.
[8] Vorhoeve, N.: Jour. de radiol. et electrol., 1919, iii, 414.
[9] Rumpell: Centralbl. f. Chir., 1902, xxix, 1091.
[10] Arch. f. klin. Chir., 1914, cv, 676.
[11] Ztschr. f. Urol., 1911, v, 586.
[12] Oehler: Beitr. z. klin. Chir., 1914, lxxxix, 223.
[13] Beitr. z. klin. Chir., 1889, iv, 197.
[14] Tr. Am. Assn. Gen.-Urin. Surg., 1913, viii, 289.
[15] Loc. cit.
[16] Centralbl. f. Chir., 1902, xxix, 1091.
[17] Ann. Surg., 1901, xxiv, 581.

Newman[18] diagnosed horseshoe kidney by palpation and attempted removal of a stone by the transperitoneal route.

Krotoszyner[19] operated on a patient with bilateral nephrolithiasis in which the pyelogram showed no abnormality. Horseshoe kidney with pyonephrosis was encountered. One stone was removed, with death in five days from uremia and sepsis. The lumbar incision was employed.

The most recent case recorded is the interesting one of Primrose,[20] where the patient presented a palpable tumor of the abdomen. Operation revealed a horseshoe kidney, of which one organ was consumed by a malignant cyst in which many calculi were found. The calculi were removed and the patient survived nine months. In dealing with this condition, Primrose sutured together the margins of the incisions in the anterior and posterior parietal peritoneum, thus marsupializing the mass.

PROTOCOL OF CASE. J. A., white, male, a hatmaker, aged twenty-nine years, was admitted to the University Hospital, Philadelphia, April 6, 1920.

Two years previously patient began to have a pain in his left lumbar region. The pain was sharp but not of great severity, and would last from a few hours to several days. There was no radiation of pain and no urinary symptoms.

In August, 1919, patient had a very severe attack of pain in the left lumbar region, with radiation to the left testicle. Patient was forced to go to bed. The pain lasted several days, and for two days thereafter the urine was reddish. Since then the patient has had four similar attacks. With them there is urgency but no pain or frequency. Between the attacks patient has a constant, dull pain in the left lumbar region but which does not radiate.

There are no symptoms referred to the other systems and the past medical history is negative.

Examination reveals a well-muscled Italian, in evident good health. Positive findings are as follows:

Severe pyorrhea; slight cervical adenopathy; epitrochlear glands are palpable; a few scattered rales at the left base.

The lower pole of the left kidney is vaguely palpable and slightly tender. The upper left quadrant of the abdomen is slightly resistant to palpation. About one inch to the left of the umbilicus, and on a level with it, there is well-defined tenderness. Pressure over the corresponding spot on the right side causes sharp pain in the left hypochondrium.

Blood-pressure 130–75.

The urine shows 10 to 12 red blood cells and 8 to 10 white blood

[18] Lancet, 1917, ii, 236.
[19] Ann. Surg., 1917, lxv, 565.
[20] Jour. Am. Med. Assn., July 3, 1920, lxxv, 12.

cells per high-power field, with a trace of albumin, and occasional hyalin casts. The blood count is normal. Phthalein elimination (intramuscular) is 37 per cent. in the first hour and 20 per cent. in the second hour.

Cystoscopy (Dr. Alexander Randall) discloses an entirely normal bladder and ureteral orifices. No difficulty was encountered in injecting the contrast fluid into the kidney pelvis, and it stayed in position readily.

The roentgen ray shows a stone about 1.5 cm. in diameter in the left kidney. Pyelogram shows both pelves slightly distended and several calices of the left pelvis pointing forward toward the spine, suggesting rotation (Dr. Henry Pancoast).

A diagnosis of stone in the left kidney was made.

Operation, April 9, 1920. Left lumbar incision. The upper pole of the left kidney was exposed and freed without difficulty. The lower pole, however, could not be dislocated even after prolonging the incision downward. On palpation it appeared lower than normal, and it could be felt extending across the lumbar vertebræ. Since it was evident that a horseshoe kidney had to be dealt with, it was deemed advisable to approach the kidney by another route and the incision was closed around a cigarette drain.

Convalescence was uneventful. Two weeks after operation the patient had a severe attack of renal colic which lasted for about twenty-four hours, and three weeks later a second attack of like severity was experienced. Roentgen ray showed the stone in its original position.

Operation, June 4, 1920. Dr. John B. Deaver. A left rectus incision was made. The great omentum and the intestine were moved out of the field to the right. The sigmoid was found to have an unusually short mesentery. An incision was made in the outer leaf of the descending mesocolon and the descending colon was mobilized and pushed to the right. The left ureter was identified where it crossed the left iliac artery. The ureter was traced upward until the pelvis and lower pole of the left kidney were reached. The lower pole of the left kidney was found to be continuous with that of the right by an isthmus about 8 cm. in width.

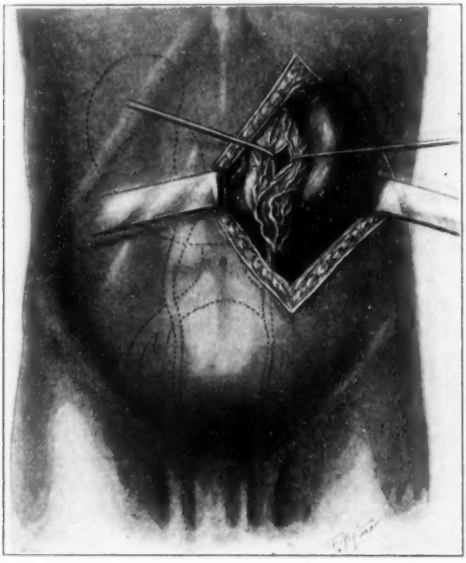
The pelvis of the left kidney overhung the left kidney in a ventral position. It was distended to about twice its normal size. Encircling the upper part of the left ureter several large anomalous veins ramified over the pelvis. The artery was posterior to the ureter and the veins.

The upper pole of the left kidney was disclosed and mobilized. No stone could be felt in the pelvis. An incision was made between two large veins and the finger detected a stone in one of the uppermost calyces. The stone was removed. It was about 1.5 cm. in diameter and of the mulberry type. The pelvis was closed with

inverting Lembert sutures. Two rubber drainage tubes were put through the lumbar scar. The posterior parietal peritoneum was sutured and the abdomen closed without drainage.

Convalescence was rapid and uneventful. There has been no recurrence of symptoms to date.

The case is of particular interest in that from the abdominal signs the possibility of horseshoe kidney should have been entertained. It also emphasizes the fact that a difficult or impossible procedure through the lumbar route may be converted into a comparatively simple one by employing the transperitoneal route.



Conclusions. 1. The possibility of horseshoe kidney must be borne in mind in kidney cases which exhibit a caudal position of the kidneys and abdominal pain or tenderness.

2. The transperitoneal operation is the operation of choice in dealing with horseshoe kidney.

3. If a horseshoe kidney is encountered upon lumbar operation and moderate efforts fail to dislocate it, it is advisable to defer further efforts rather than to make an enlarged and mutilating incision.

INFECTION OF THE KIDNEYS FOLLOWING PROSTATECTOMY.

By John W. Marchildon, B.S., M.D., F.A.C.S.,
GENITO-URINARY SURGEON TO THE ALEXIAN BROTHERS' HOSPITAL; ASSISTANT PROFESSOR, ST. LOUIS UNIVERSITY SCHOOL OF MEDICINE.

While measures have been taken in recent years in the preparation and after-treatment of prostatics, tending to prevent uremia and hemorrhage, no special emphasis has been placed upon infection as a cause of death. Almost all cases of hypertrophy of the prostate suffering with urinary retention have an infected bladder. In case of immediate prostatectomy the infection is very liable to spread to other parts of the body and most frequently it ascends to the kidneys producing a pyelonephritis. There is a certain important group of cases, however, in which the urine is clear and sparkling, with no infection of the bladder and with only a small amount of retention, and it is in just these cases that a complete prostatectomy, done in one stage, may result in death. Even though the bladder is not infected at the time of operation it readily becomes infected when it is opened and pyelonephritis may be the fatal outcome. The raw, torn area from which the prostate is removed offers a most favorable area for absorption, for the entrance of microörganisms into the circulation and for the spread of an ascending infection to the kidneys.

The dangers following the operation of prostatectomy, named in the order of their occurrence, are said to be shock, toxemia, hemorrhage, uremia and later possibly pulmonary complications. Of these dangers uremia is said to be the most frequent cause of death, with hemorrhage as a close second. Symptoms of impaired kidney function called uremia clinically are said to produce about one-fourth of the deaths.

Uremia is not an exact diagnosis, and in most cases of so-called uremia following prostatectomy at autopsy a pyelonephritis is found. The various symptoms which manifest themselves in the clinical condition, however, may be dependent upon compensation of the cardiovascular system, and we are wont to associate it with the idea of a decreased amount of kidney cortex. Uremia due to a nephritis, in which the secreting cells of the kidneys are decreased and changed by an inflammatory and toxic increase of connective tissue, is not a frequent cause of death following prostatectomy. It is not always easy to distinguish clinically between uremia resulting from non-infective conditions as a cause of death and that due to a pyelonephritis and general infection. A patient may have a toxemia, be poorly nourished and secrete a urine of very low specific gravity, and death may ensue with the patient in a state of uremia. However, in such a case an infection may be the basic

cause and may be located in the kidneys in the form of a pyelitis or pyelonephritis.

In the consideration of the postmortem examinations that I have made on my cases at the Alexian Brothers' Hospital, St. Louis, following prostatectomy, infection in the form of a pyelonephritis has been a more frequent cause of death than any other factor. In those cases in which uremia has been a cause of death, clinically, a postmortem examination has shown the presence of an infection in the kidneys. The urinary bladder which has been infected in almost all cases of this type would seem to be the starting-point for the production of a pyelonephritis and septic infection.

Infection of the kidneys following prostatectomy is more frequently the cause of death than is at present considered to be the case. In my cases it has increased the mortality more than any other single factor. These patients suffering with prostatism are individuals advanced in age and in whom focal infection is very liable to be present in some distant parts of the body which may readily be lighted up by the weakened condition resulting from urinary retention and the following operative procedures: Infection of the kidneys may follow prostatectomy or may be present before the prostatectomy is done. Since catheterization of the ureters is difficult and cannot always be performed, very valuable information is given by a careful roentgen-ray examination. It is my custom to ray the kidneys as a routine measure, and with proper technic their form may be shown in every case. The best means of relieving infection of the urinary bladder is prolonged drainage. As a rule, when the patient fails to improve with free bladder drainage an infection in some other part of the body is present. An infection is most often located in the kidneys in these prostatics and is responsible for their failure to gain in strength. Whether or not preliminary cystotomy should be carried out I am of the opinion it should be done in all cases. A careful preparative period of a few months of the patient has gradually reduced the frequency of pyelonephritis and has lessened the mortality of operation. This preparation should also be directed toward resisting infection and continued as long as an infection remains.

Following the institution of free bladder drainage when the patient has improved as much as it is possible to make him improve, then the second stage of the prostatectomy should be carried out. It would also be reasonable to think that in a case of hypertrophy of the prostate, if the urine is clear and shows no pus and cultures show that the urine is sterile, the prostatectomy could be done in one stage, other things being equal. This is not true because it is in just these cases that the mortality is high in the one-stage operation. The urinary bladder in such a patient is called upon to resist an infection, when the patient has developed very little immunity, along with all the other dangers incident to the operation.

It is advisable to make cultures of the bladder urine in all cases of hypertrophy of the prostate. In those cases on the genito-urinary service at the Alexian Brothers' Hospital, St. Louis, in which a prostatectomy was done and an infection of the urinary bladder was present, the microörganisms isolated by culture from the urine were the colon bacillus, streptococcus, and the staphylococcus. The urine has contained varying amounts of pus from a few cells to large quantities of thick, creamy pus. In making cultures from the urine of cases of hypertrophy of the prostate, even though it is clear and sparkling, the colon bacillus and staphylococcus may be found.

It is advisable to make a cystoscopic examination in every case before operation. This examination cannot be made at once, as preparatory treatment is necessary before it is undertaken. Most patients that enter the hospital suffer with urinary distress and retention of urine, and as catheterization may be very difficult or impossible, it is frequently necessary to make a suprapubic opening in order to relieve the retention of urine. Frequently patients have a severe cystitis with calculi, rendering the bladder difficult of distention for examination. The prostatic urethra does not readily admit the cystoscope in this condition. The cystoscope may be passed through the suprapubic opening, the bladder being filled with water, and valuable information may be obtained in this way. By means of this the condition of the bladder wall as regards inflammation or tumor is seen and also the presence of a stone in the bladder, which is quite common in patients who have led a catheter life, or the fact of the presence of any foreign body in the bladder is learned. Information as to the size of the gland and the condition of the vesical neck, as to whether or not a prostatic bar is present, or whether the neck is contracted, is gained. It shows the amount of trabeculations of the bladder and the presence of any diverticuli. A cystoscopic examination, therefore, may show the cause of the prostatism, of which the patient complains.

From the review of the cases on my service the necessity of free bladder drainage and the treatment of the resisting infection is apparent, and it would seem to be the most important factor in the preliminary preparation of the patient for prostatectomy. It is possible to carry this out in a fair proportion of cases by means of systematic catheterization or by means of the retained catheter, but drainage of the bladder in this manner is not as perfect and does not give as good results as with a suprapubic cystotomy. There were a large number of cases in which the catheterization could be performed only with great difficulty. In all of my cases in which a retention catheter was used it was not borne well. In all badly infected cases the infection clears up more slowly, and such patients do not get along as well as when a suprapubic drainage is instituted. The patients that have gone to autopsy, when drained suprapubically were not drained for a very long period of time and the infection

still remained, or they have died from causes in no way dependent upon their urinary condition. Those patients that have recovered have been those that were drained for longer periods of time. Desperate cases in whom the preliminary suprapubic drainage was carried out at once, and the drainage continued for a month or longer, and in whom treatment for the existing infection was given have nearly always recovered.

Preliminary suprapubic drainage relieves the back pressure on the kidneys and permits a successful treatment of the infected bladder. In this way the absorption of the toxic products from the urinary bladder ceases and it is shown by the improved general condition of the patient. It is also seen in the decrease of the infection and by the diminution of the congestion and engorgement of the prostate gland. The gland becomes smaller in size as the infection clears up and its removal is made much more easy. The amount of bleeding during its enucleation is lessened and the raw, torn surface which remains after the removal of the gland is smaller than would ordinarily be the case. It follows, therefore, that the amount of absorption of toxic material following the operation is less than when a complete removal is done at once, when the prostate is of larger size.

Even though the urinary bladder is not infected and the urine is sterile to culture it becomes infected very soon after a suprapubic cystotomy is done. A prostatectomy done in one stage upon such a case may be followed by death and an autopsy shows a pyelonephritis to be the cause. Such a patient is called upon to reisst infection at the same time with all the other factors incident to the operation. If in such a case the bladder be opened and free drainage instituted the individual has to combat only the infection which is acquired. A few weeks of free bladder drainage following the suprapubic cystotomy enables the patient to establish an immunity to infection by way of the urinary bladder. It is when this resistance has been established that the second stage of enucleation of the prostate may be carried out with little danger of a fatal infection of the kidneys resulting.

Hemorrhage following prostatectomy has been given considerable attention, and especially has it been emphasized as a cause of death. To control hemorrhage, Hagner has introduced a rubber bag. Kolischer has described the removal of the prostate through an incision after which he implants a piece of fat and sews up the incision to control hemorrhage, and many others emphasize the necessity of packing the cavity of the prostate with iodoform gauze. All of these measures have as their object the control of hemorrhage. It has been my custom in my work to give very little attention to hemorrhage. It has not been a cause of death in a single case. There is very little bleeding, especially if the patient has been given prolonged preparation for operation by drainage of the bladder for a long period of time. The anatomical conditions are such that there

are very few bloodvessels above where the enucleation of the prostate is begun and as the finger finds the proper line of cleavage, the lobes of the prostate are freed readily and the prostate is delivered with very little bleeding.

A study of the records of those cases in which a prostatectomy was done on the genito-urinary service of the Alexian Brothers' Hospital, St. Louis, and in which the cause of death was determined by a postmortem examination shows that an infection of the kidneys in the form of pyelonephritis was the most frequent cause of death. The greater number of deaths occurred when a complete prostatectomy was done in one stage. Death, however, has occurred following the first stage. The records for study may be classified as those cases in which death followed as a result of prostatectomy and those in which the fatal outcome was in no way dependent upon conditions due to operation.

An example of a case in which the patient had a clear sparkling urine, though with retention, and following a complete prostatectomy in one stage, death was caused by a pyelonephritis, is the following:

J. E. S., aged sixty-eight years, entered the Alexian Brothers' Hospital, December 30, 1918. On admission he had complete retention and a large prolapse of the rectum. Difficulty in urination for over two years has been present. He complained that urination was always prolonged, but there had never been any pain or burning. He had gradually been losing in weight but has had no previous urinary distress. On examination he was considerably emaciated. The prostate was very large, smooth and firm. He was given bladder irrigations daily and large quantities of nutritious fluids. A retention catheter was placed in the bladder but was not well borne. The following day on catheterization he had a residual of 100 c.c. The prolapsus had disappeared on systematic catheterization. The urine from the bladder was clear, sparkling and contained no pus, albumin nor casts. The general appearance and condition of the patient gradually improved. The phthalein output eight days after admission was 45 per cent. the first hour and 28 per cent. the second hour. The non-protein nitrogen was 65 per cent. per 100 c.c. of blood. His blood-pressure showed an average of 135 systolic and 95 diastolic. The leukocyte count was 8200. The total output of urine in twenty-four hours was 1800 c.c., with a specific gravity of 1.018. Nine days after admission the patient had 30 c.c. residual urine. He had improved in strength and apparently in resistance. He looked well and an examination of the heart and lungs was negative. On the eighth day the patient was given ether and the prostate was enucleated, the operation being done in one stage. The patient got along fairly well for four days following the operation, when his temperature suddenly rose to 105° F. and his pulse to 120. There was no pain present over the kidneys. The patient became uremic and hiccough developed. The tongue

was coated and dry. The skin was dry, the stupor increased and the patient became comatose and died the following day. At autopsy the anatomic diagnosis was: acute pyelonephritis, acute splenitis, acute degenerative myocarditis and edema of the lungs.

As an illustration of a case in which the patient had an infected bladder, with retention of urine and in which death was due to a pyelonephritis following a complete prostatectomy in one stage, I quote as follows:

C. B., aged eighty years, entered the Alexian Brothers' Hospital, St. Louis, May 2, 1919. On admission to the hospital he had a complete retention. A soft-rubber catheter was passed and 500 c.c. of cloudy purulent urine was evacuated. Patient has had difficulty in urination for the past three years and at five different times has had complete retention and had been relieved by catheterization. The last attack of complete retention was one month ago. Before these attacks of retention he had an attack of frequency and burning on urination. For the past three years the patient has had difficulty in breathing, and shortness of breath with pain in the region of the heart. Numerous hemorrhoids were present with a prolapsus ani. Irrigations of the bladder were instituted and a retention catheter was tied in. At the end of two weeks the patient had improved in appearance. The urine, however, still contained a large amount of pus. His combined phthalein output was 30 per cent. for the first hour and 12 per cent. for the second hour. The non-protein nitrogen was 120 per cent. for 100 c.c. of blood. The clinical diagnosis was hypertrophy of the prostate with retention of urine, cystitis with calculi of the urinary bladder, chronic myocarditis, pulmonary emphysema, chronic nephritis and cataract of the left eye. The patient had improved in appearance, and in strength, however, his retention of urine was complete. On leaving out the retention catheter he was unable to void. The improvement was such that prostatectomy in one stage was decided upon. The following day he was given ether and a complete prostatectomy in one stage performed. Following the operation the patient got along well. On the morning of the fourth day he developed a temperature which increased progressively, and by night was 105° F. He became dull, the tongue dry and he had a septic appearance. The leukocyte count was 12,000. A blood culture showed no microörganisms. Blood-pressure was 130 systolic and 90 diastolic. Pulse was 130 and full. The abdomen was soft and there was no pain or tenderness elicited by deep palpation over the kidneys. Death occurred the following day. The anatomic diagnosis was advanced pyelonephritis of both kidneys, acute splenitis and acute degenerative myocarditis.

It has been said that if a prostatic survives the preliminary operation of opening the bladder he will survive the second stage of removal of the prostate gland. This is not always the case. A

prostatic may die following the second stage of a two-stage prostatectomy from the usual cause of death, a pyelonephritis. This was true in a case in which the time of drainage of the bladder was short:

J. H. S., aged seventy-six years, was admitted to the Alexian Brothers' Hospital, April 6, 1920. On admittance to the hospital the patient was suffering with a complete retention of urine. He was in bad physical condition when admitted. Catheterization had been attempted repeatedly before admission and had failed, but in the hospital catheterization was successful and 500 c.c. of bloody, purulent urine was drawn off. The patient states that his urinary disturbance was of five years' duration and that this was his first attack of complete retention. He has suffered from shortness of breath and edema of the ankles at times. Examination showed a large smooth, boggy, movable prostate. With the exception of large hemorrhoids the rectum was free. Patient had a mitral insufficiency of moderate degree with an accentuation of the second aortic. He was uremic. The urine was scanty and contained albumin, pus cells and granular casts. He had edema of both legs and a cataract in both eyes. The clinical diagnosis on admission was retention of urine due to hypertrophy of prostate, chronic nephritis, mitral endocarditis, chronic myocarditis and cataract. The phthalein output was 22 per cent. for the first hour and 9 per cent. for the second hour. The non-protein nitrogen was 135 for 100 c.c. of blood. The catheter met a marked obstruction in the prostatic portion of the urethra and could only be passed with great difficulty, so that three days after admission a suprapubic cystotomy was performed under local anesthesia and a drainage tube was tied in place. A general improvement set in at once and twelve days following the suprapubic cystotomy the patient appeared to be in good condition. He had regained strength and resistance and looked well. A cystoscopic examination showed a moderate cystitis and a large bulging prostate within the bladder neck. A rectal examination showed the gland to be smaller and more firm than on admission. The urine still contained pus and a variety of microorganisms. The total urine in twenty-four hours was 1400 c.c. with a specific gravity of 1.016. The phthalein output for the first hour was 38 per cent. and for the second hour 18 per cent. The non-protein nitrogen was 120 per cent. per 100 c.c. of blood. The blood-pressure was on an average of 138 systolic and 90 diastolic. The temperature was normal. Edema of the legs had disappeared. Patient was able to walk about and did not remain in bed during the day. The examination of the heart and lungs showed pulmonary emphysema and mitral insufficiency, with arteriosclerosis, which were recognized on admission. On the twelfth day following the suprapubic cystotomy the patient was given ether and the prostate was enucleated. Following the second operation he did not do well. Four days later there was a sweet odor to the breath and he had

developed hiccough. His tongue was brown and dry and there was a tinge of icterus to the skin. Patient developed dyspnea. The temperature was 103° F. The following day the apex beat was diffuse and there was no muscular tone. The blood-pressure was 103 systolic and 104 diastolic. The temperature rose to 105° F., pulse to 138 and respiration to 50. The abdomen was lax. There was no tenderness present over the kidneys. The liver was not palpable. Symptoms gradually progressed and the patient died in coma. At autopsy the anatomic diagnosis was advanced pyelonephritis, acute myocarditis, acute bronchitis and chronic pulmonary emphysema.

A prostatic may also die following the second stage of a two-stage prostatectomy from a condition in no way dependent upon the operation.

An example of this is the following case:

L. B., aged seventy-eight years, admitted to the Alexian Brothers' Hospital, St. Louis, June 23, 1918. At the time of admission to the hospital he had complete retention of urine and was in a semi-comatose condition. Catheterization yielded 600 c.c. of bloody purulent urine. Examination showed a large, soft, prostate which was not fixed. Hemorrhoids were present. Patient was emaciated. The chest was barrel-shaped and a marked scoliosis was present. The specific gravity of the urine was 1.008 and numerous red blood corpuscles, pus cells and granular casts were present. The clinical diagnosis was hypertrophy of the prostate with retention of urine, chronic nephritis, chronic myocarditis, chronic bronchitis and arteriosclerosis. The retention catheter could not be kept in the bladder, so it was determined the following day to perform a suprapubic cystotomy in order to give free bladder drainage at once. This was done under local anesthesia and a large drainage tube was tied in. With free bladder drainage the patient rapidly improved and was able to give an accurate history of his condition. For over five years patient had returned to the hospital at various intervals with retention of urine. By systematic catheterization and bladder irrigations, patient had left each time feeling comfortable. Fourteen days following the first-stage operation patient had generally improved and was walking about. Cystoscopic examination at this time showed a large nodular prostate. The bladder showed numerous trabeculations. The urine from the bladder contained numerous microörganisms, pus cells and granular casts. Phthalein appeared in the urine after seventeen minutes. The total output the first hour was 32 per cent. and the second hour was 17 per cent. The non-protein nitrogen was 120 for 100 c.c. of blood. The blood-pressure was systolic 157 and diastolic 80. The total quantity of urine in twenty-four hours was 3700 c.c., with a specific gravity of 1.002. The leukocyte count was 10,400. The temperature was 98.6° F., respiration was 22. Patient had gained fifteen pounds

in weight. Fourteen days following the first stage operation he was given ether and the prostate enucleated. Within twenty minutes the patient had been returned to bed and was in excellent condition. On the fifth day following the operation the temperature and respiration were normal and the pulse was 110 and somewhat irregular. There was no hemorrhage; the urine was not bloody. The large suprapubic drainage tube had been removed and a smaller one had been instituted. The patient was rational. Respirations were thirty. There was a certain amount of dyspnea present. Twelve hours later the dyspnea was very great. The pulse was very rapid and thready. The apex-beat was diffuse and the patient had labored breathing. There was edema of the ankles present. Patient was given stimulation and water was increased as much as he would take. The dyspnea increased rapidly and the heart action became weaker and death occurred the following day. At the autopsy the diagnosis was mitral endocarditis with insufficiency. Chronic myocarditis, edema of both lungs, chronic passive congestion of the liver and spleen and chronic nephritis.

The case records which are quoted here are typical of their class and the autopsy findings are representative of what is found as a cause of death. No effort has been made to determine the mortality rate. The death-rate from prostatectomy has not been higher than with other individuals and institutions. More recently there have been fewer deaths, and I have attributed it to a better understanding of the presence of infection in the form of pyelonephritis which threatens prostatics, and to a prolonged, free, suprapubic drainage, and treatment for infection in their preparation for operation.

URINARY ANTISEPSIS: A STUDY OF THE ANTISEPTIC PROPERTIES AND THE RENAL EXCRETION OF 204 ANILIN DYES.[1]

By Edwin G. Davis, M.D.,

OMAHA, NEB.

In 1915 Hinman[2] pointed out the inefficiency of the several drugs at present in common use as urinary antiseptics and concluded that there is no known drug ideally suited for this purpose or even approaching the ideal. These observations are borne out by the experience of everyone who has had to deal with chronic infections of the urinary tract and also by the absence in the literature of conclusive experimental or clinical evidence of the fitness of any drug

[1] Investigations were carried on in the laboratory of the University of Nebraska College of Medicine, with the aid of an appropriation made by the United States Interdepartmental Social Hygiene Board.

[2] Urinary Antisepsis: A Clinical and Bacteriological Study, Jour. Am. Med. Assn., 1915, lxv, 1769.

for this purpose. The ideal internal urinary antiseptic should be chemically stable and relatively non-toxic and non-irritating; should be antiseptic in high dilution in urine as well as on agar (regardless of the reaction of the former), and should be eliminated in high percentage by the kidney without injury to the body. Clinically there is no such drug known.

For the purpose of urinary antisepsis, urotropin is the most widely used, and likewise the best suited available drug, on account of its well-known and proved action of liberating formalin in the urine. Urotropin, however, has very definite limitations, owing largely to the necessity for an acid urine for the liberation of formalin, and this becomes an insurmountable obstacle in those urines infected with alkalinizing organisms, such as the micrococcus urea or bacilli of the proteus group. As is well known, by the administration of acid sodium phosphate it is possible to cause a temporary slight increase in urinary acidity.

Henderson and Palmer[3] have shown, however, that even after the administration of 10 grams of acid sodium phosphate at a single dose there follows only a slight increase in the hydrogen ion concentration, and in no case were they able to produce a urinary acidity greater than that which they had commonly observed in patients to whom no drug had been administered. On the other hand to produce and maintain a relatively large variation toward the alkaline end of the hydrogen ion scale, by the use of sodium bicarbonate, is comparatively simple. Therefore, granting that the efficiency of a given urinary antiseptic must necessarily be dependent upon the reaction of the urine, a drug efficient in alkaline urine only would be of greater practical value than is urotropin.

Another recognized limitation to urotropin is the time necessary for formalin liberation (Burnam[4]), which destroys the value of the drug at the kidney level and also in the bladder in cases in which for any reason there is rapid emptying or where a fistula exists. The main value of urotropin lies in its use as a prophylactic before instrumentation.

Summary of Previous Studies. Previous publications record the results of investigations with reference to the synthesis of an internal urinary antiseptic, carried on at the Brady Urological Institute, Johns Hopkins Hospital, in coöperation with Dr. Edwin C. White, chemist for that institution. (Davis,[5] Davis and White,[6] Davis,

[3] On the Extremes of Variation of the Concentration of Ionized Hydrogen in Human Urine, Jour. Biol. Chem., 1913, xiv, 81.

[4] An Experimental Investigation of the Value of Hexamethylenamin and Allied Compounds, Arch. Int. Med., 1912, x, 324.

[5] Urinary Antisepsis: A Study of the Antiseptic Properties and Renal Excretion of Compounds Related to Phenolsulphonephthalein: Preliminary Report, Jour. Am. Med. Assn., 1918, lxx, 581.

[6] Urinary Antisepsis: Further Studies of the Antiseptic Properties and Renal Excretion of Compounds Related to Phenolsulphonephthalein, Jour. Urol., 1918, ii, 107.

White and Rosen[7]). Here an attempt was made to correlate chemical structure with the antiseptic properties and the renal excretion of the compounds studied, most of which were synthesized for this special purpose, with the hope that the introduction of certain groups into the molecule would produce certain desired properties. The study was limited largely to compounds related to phenolsulphonephthalein, because of the well-known extraordinary "renal affinity" possessed by this compound and because of its non-toxicity. Some interesting results were obtained which may be briefly summarized as follows:

1. It was possible to establish a certain relationship between chemical structure and renal excretion and to predict the excretion of molecules of certain structure, particularly those of the xanthone group. The halogenation of these compounds interfered with excretion.

2. Many of these compounds, non-toxic, excreted in the urine and antiseptic in water, lost this latter property when tested in voided urine.

3. One compound, chlor-mercury fluorescein, experimentally possessed all of the required properties, and when administered intravenously in minute dosage (5 mgm.) to dogs and rabbits caused the secretion of antiseptic urine for a definite period of time without injury to the animal.

Clinical investigation of this drug has not been carried out on account of its mercury content, although it was shown that in dogs the single lethal dose was forty times that necessary to cause the secretion of antiseptic urine. Chlor-mercury fluorescein, therefore, approaches the ideal in that (*a*) it is antiseptic in high dilution in either acid or alkaline urine; (*b*) it is excreted by the kidney with a rapidity as great as is phenolsulphonephthalein, and (*c*) experimentally efficient dosage may be administered without toxicity. Chlor-mercury fluorescein is an organomercury phthalein derivative in which the mercury is present in non-ionic form.

4. Continued experiments along the same lines (Davis and White[8]) have shown that acriflavin and proflavin are antiseptic in high dilution in urine (particularly in alkalin urine) and that intravenous administration of minute dosage (5 mgm. per kilo) to rabbits causes secretion of urine, which is antiseptic for a definite period of time without injury to the animal. Rabbit urine is normally usually alkaline. Failure to produce antiseptic urine in dogs with corresponding dosage of the same drug was probably due to the fact that dog urine is usually acid (average about p_h, 6).

[7] Urinary Antisepsis: The Secretion of Antiseptic Urine Following the Intravenous Administration of an Organomercury Phthalein Derivative, Jour. Urol., 1918, ii, 277.

[8] Davis, E. G., and White, E. C.: Urinary Antisepsis: The Secretion of Antiseptic Urine Following the Intravenous Administration of Acriflavin and Proflavin, Preliminary Report, Jour. Urol., 1918, ii, 299.

Possibilities Offered by Anilin Dyes. The following record summarizes the results of an investigation of the antiseptic properties and the renal excretion of 204 anilin dyes, the scope of the work being limited and guided, not by the chemical structure of these compounds but only by the number available. This investigation was carried on in the laboratories of the University of Nebraska College of Medicine with the aid of an appropriation made by the United States Interdepartmental Social Hygiene Board.

The anilin dyes were chosen for study (1) because of the large number of these compounds available, (2) because of their color and hence their ready detection and quantitative estimation in the urine and (3) because, through the work of many observers (notably, Churchman,[9] Krumwiede and Pratt,[10] Simon and Wood,[11] Kligler,[12] Graham-Smith[13]), the antiseptic properties of certain anilin dyes have become well known and therapeutic possibilities in this field have been indicated. Furthermore a consideration of the history of the development of the various tests of renal function (Thomas and Birdsal[14]) will call to mind that there are several dyes (fuchsin, rosanilin, indigo-carmin, uranin, trypan blue and others) which have been used to measure the functional activity of the kidneys, and which are therefore known to be excreted without injury to the patient. The staining and penetrating properties possessed by many anilin dyes likewise suggest suitability of this type of compound for medication of the urethral mucosa. This investigation was not undertaken without due realization of the handicap presented by impurities in commercial samples of anilin dyes.

Method of Investigation. Considering the large number of dyes to be studied it was advisable to select a few by preliminary test on agar, thus ruling out many as being unworthy of further investigation. The remaining few were then studied in regard to their antiseptic value in urine, their toxicity, their renal excretion and in regard to their ability to cause the secretion of antiseptic urine following intravenous administration. Finally, those few which were found to be particularly efficient against the staphylococci were tested on special media against the gonococcus. (Tables showing results with the gonococcus will appear in a subsequent publication.) The investigation was therefore divided into five stages as follows:

[9] The Specific Antiseptic Action of Gentian Violet Corresponding to Gram, Jour. Exper. Med., 1912, xvi, 221, 822.

[10] Observations on the Growth of Bacteria on Media Containing Various Anilin Dyes, Jour. Exp. Med., 1914, xix, 20 and 501.

[11] The Inhibitory Action of Certain Anilin Dyes upon Bacterial Development, Am. Jour. Med. Sc., 1914, cxlvii, 247.

[12] A Study of the Antiseptic Properties of Certain Organic Compounds, Jour. Exp. Med., 1918, xxvii, 463.

[13] Some Factors Influencing the Actions of Dyes and Allied Compounds on Bacteria, Jour. Hyg., 1919, xviii, 1.

[14] Comparative Results of Various Functional Renal Tests, Based on a Series of Cases, Jour. Am. Med. Assn., 1917, lxix, 1747.

1. *Antiseptic Values on Agar.* Determination of the antiseptic strength of the entire list of dyes on agar against B. coli, Staphylococcus albus and Staphylococcus aureus.

2. *Antiseptic Values in Urine.* Determination of antiseptic strength of selected dyes in both acid and alkaline urine against B. coli, S. albus and S. aureus.

3. *Toxicity and Excretion.* Determination of toxicity and renal excretion in rabbits of dyes shown to have antiseptic value in voided urine.

4. *Experimental Urinary Antisepsis.* Determination of the antiseptic value of the urine of rabbits which had received intravenous injections of dyes previously shown to be non-toxic and excreted.

5. *Inhibition of Gonococcus.* Determination on special media of the antiseptic strength against the gonococcus of those dyes which had been shown to inhibit the staphylococcus in high dilution.

1. *Antiseptic Values on Agar.* Preliminary antiseptic tests were carried out on the entire list of dyes, using agar neutral to phenolphthalein and of the following composition:

Agar	15 gm.
Peptone (Witte)	10 gm.
Meat extract (Liebig)	5 gm.
Sodium chloride	5 gm.
Water	1000 c.c.

Since the colon bacillus is by far the most frequent invader of the urinary tract, this organism was chosen together with S. albus and S. aureus. The agar was autoclaved in test-tubes in 9 c.c. amounts, after which 1 c.c. of an aqueous solution of the dye was added, the latter solution being at a concentration ten times that desired for the final dilution. Each dilution was then plated, cooled and inoculated by three parallel strokes from twenty-four-hour broth cultures of the three above-named organisms. No concentrations greater than 1 to 1000 were used, all dyes not showing antiseptic properties at this concentration being discarded. The selective antiseptic action against various organisms which Churchman has described, with particular reference to gentian violet, was exhibited by no less than 44 dyes, and in every case it was the colon bacillus that survived, while one or the other of the staphylococci (usually both) failed to grow. (See Figs. 1, 2 and 3.)

2. *Antiseptic Values in Urine.* As previous publications on this subject have indicated the possession of antiseptic properties by a drug when diluted in water or in agar is no indication whatever of its antiseptic value when diluted in urine. Many of the sulphonephthaleins which were germicidal in high dilution in water lost this property when diluted in urine in a test-tube and even permitted the growth of organisms in urine when in relatively high concentration. In determining the antiseptic value in urine of the dyes selected by preliminary test on agar it was therefore desirable to

Possibilities Offered by Aniln Dyes. The following record summarizes the results of an investigation of the antiseptic properties and the renal excretion of 204 aniln dyes, the scope of the work being limited and guided, not by the chemical structure of these compounds but only by the number available. This investigation was carried on in the laboratories of the University of Nebraska College of Medicine with the aid of an appropriation made by the United States Interdepartmental Social Hygiene Board.

The aniln dyes were chosen for study (1) because of the large number of these compounds available, (2) because of their color and hence their ready detection and quantitative estimation in the urine and (3) because, through the work of many observers (notably Churchman,[1] Arnold and Pratt,[2] Simon and Woodyatt,[3] Klieger,[4] Graham-Smith[5]), the antiseptic properties of certain aniln dyes have become well known and therapeutic possibilities in this field have been indicated. Furthermore, a consideration of the history of the development of the various tests of renal function (Thomas and Bird[6]) will call to mind that there are several dyes (fuchsin, rosaniln, indigo-carmin, uranin, trypan blue and others) which have been used to measure the functional activity of the kidneys, and which are therefore known to be excreted without injury to the patient. The staining and penetrating properties possessed by many aniln dyes likewise suggest suitability of this type of compound for medication of the urethral mucosa. This investigation was not undertaken without due realization of the hazards presented by impurities in commercial samples of aniln dyes.

Method of Investigation. Considering the large number of dyes to be studied it was advisable to select a few by preliminary test on agar, thus ruling out many as being unworthy of further investigation. The remaining few were then studied in regard to their antiseptic value in urine, their toxicity, their renal excretion and in regard to their ability to cause the secretion of antiseptic urine following intravenous administration. Finally, those few which were found to be particularly efficient against the staphylococci were tested on special media against the gonococcus. (Tables showing results with the gonococcus will appear in a subsequent publication.) The investigation was therefore divided into five stages as follows:

[1] The Specific Antiseptic Action of Gentian Violet Corresponding to Gram, Journ. Exper. Med., 1915, xxi, 221, 327.

[2] Observations on the Growth of Bacteria on Media Containing Various Aniln Dyes, Journ. Exp. Med., 1914, xix, 20 and 301.

[3] The Inhibitory Action of Certain Aniln Dyes upon Bacterial Development, Am. Journ. Med. Sc., 1914, cxlvii, 247.

[4] A Study of the Antiseptic Properties of Certain Organic Compounds, Journ. Exper. Med., 1918, xxviii, 403.

[5] Some Factors Influencing the Actions of Dyes and Allied Compounds on Bacteria, Journ. Hyg., 1916, xvi, 1.

[6] Comparative Results of Various Functional Renal Tests Based on a Series of Cases, Journ. Am. Med. Assn., 1917, lxix, 1747.

1. *Antiseptic Values on Agar.* Determination of the antiseptic strength of the entire list of dyes on agar against B. coli, Staphylococcus albus and Staphylococcus aureus.

2. *Antiseptic Values in Urine.* Determination of antiseptic strength of selected dyes in both acid and alkaline urine against B. coli, S. albus and S. aureus.

3. *Toxicity and Excretion.* Determination of toxicity and renal excretion in rabbits of dyes shown to have antiseptic value in voided urine.

4. *Experimental Urinary Antisepsis.* Determination of the antiseptic value of the urine of rabbits which had received intravenous injections of dyes previously shown to be non-toxic and excreted.

5. *Inhibition of Gonococcus.* Determination on special media of the antiseptic strength against the gonococcus of those dyes which had been shown to inhibit the staphylococcus in high dilution.

1. *Antiseptic Values on Agar.* Preliminary antiseptic tests were carried out on the entire list of dyes, using agar neutral to phenolphthalein and of the following composition:

Agar	3 gms.
Peptone (Witte)	10 gms.
Meat extract (Liebig)	5 gms.
Sodium chloride	5 gms.
Water	1000 c.c.

Since the colon bacillus is by far the most frequent invader of the urinary tract, this organism was chosen together with S. albus and S. aureus. The agar was autoclaved in test-tubes in 9 c.c. amounts, after which 1 c.c. of an aqueous solution of the dye was added, the latter solution being at a concentration ten times that desired for the final dilution. Each dilution was then plated, cooled and inoculated by three parallel strokes from twenty-four-hour broth cultures of the three above-named organisms. No concentrations greater than 1 to 1000 were used, all dyes not showing antiseptic properties at this concentration being discarded. The selective antiseptic action against various organisms which Churchman has described, with particular reference to gentian violet, was exhibited by no less than 44 dyes, and in every case it was the colon bacillus that survived, while one or the other of the staphylococci usually both failed to grow. (See Figs. 1, 2 and 3.)

2. *Antiseptic Values in Urine.* As previous publications on this subject have indicated the possession of antiseptic properties by a drug when diluted in water or in agar is no indication whatever of its antiseptic value when diluted in urine. Many of the sulphonephthaleins which were germicidal in high dilution in water lost this property when diluted in urine in a test-tube and even permitted the growth of organisms in urine when in relatively high concentration. In determining the antiseptic value in urine of the dyes selected by preliminary test on agar it was therefore desirable to

make the various dilutions with voided urine, since any drug for the above purpose would be useless unless effective in this medium. Furthermore, it was necessary to try out each dye in both acid and alkaline urines, since the ideal drug should be efficient regardless of the urinary reaction.

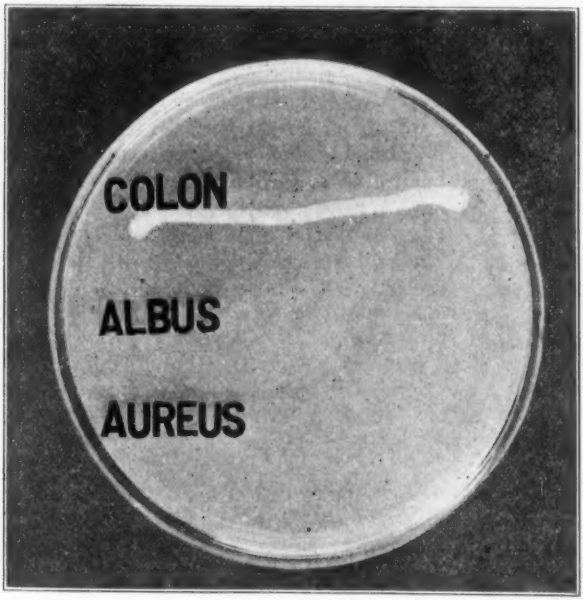


FIG. 1.—Photograph of agar plate containing chrysoidin-Y (1 to 1000), showing selective action of the dye in permitting growth of Bacillus coli and inhibiting Staphylococcus albus and Staphylococcus aureus.

In order to have available each day urine of definite acid and alkaline reaction it was necessary to titrate specimens of voided urine with tenth normal sodium hydroxide and tenth normal hydrochloric acid until definite degrees of hydrogen ion concentration were reached, as determined by the colorimetric method—that is, by comparison with a standard hydrogen ion scale made up with solutions of buffer salts colored by the sulphonephthalein series of indicators. (See publications of Clark and Lubs[15] and Shohl and Janney.[16]) On the acid side of the scale it was arbitrarily decided to use urine titrated to p_h, 6.4, which Henderson and Palmer have shown to be slightly less acid than the average reaction of normal urine. In

[15] Colorimetric Determination of Hydrogen Ion Concentration, Jour. Bacteriol., 1917, ii, 1.

[16] Growth of Bacillus Coli in Urine at Varying Hydrogen Ion Concentrations, Jour. Urol., 1917, i, 211.

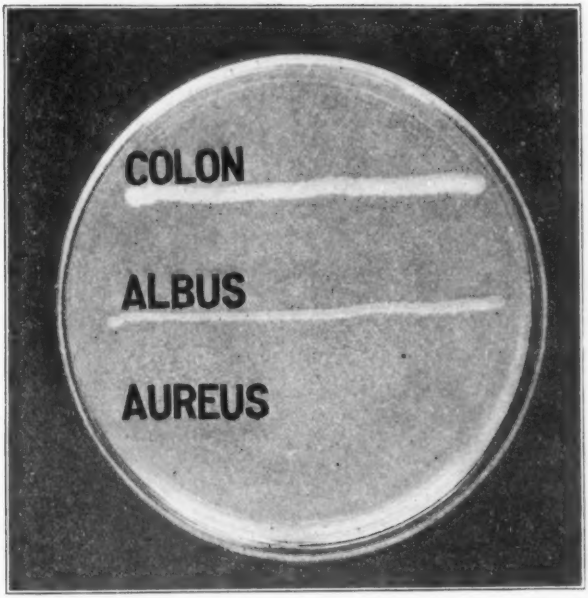


FIG. 2.—Photograph of agar plate containing phloxin-P (1 to 1000), showing selective action of the dye in permitting growth of Bacillus coli and Staphylococcus albus and inhibiting Staphylococcus aureus.

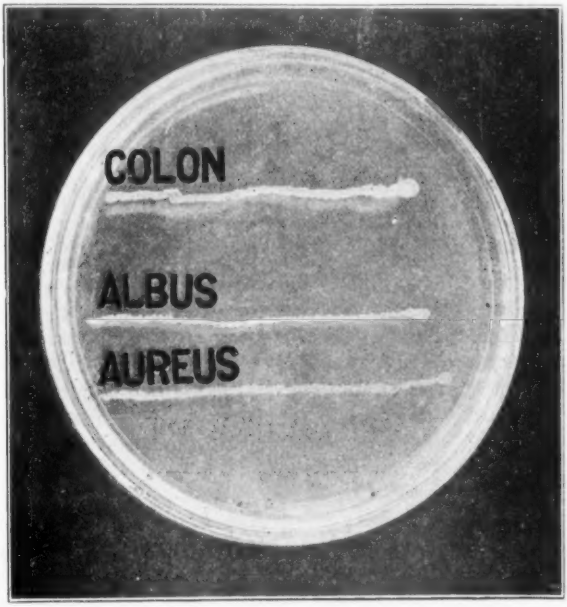


FIG. 3.—Photograph of control plate of drug-free agar, showing profuse growth of all three organisms.

order to obtain alkaline urine a sample of the same specimen was titrated to p_h, 7.6, an end-point arbitrarily chosen so that the reaction of the specimens of urine used from day to day would not vary.

Dilutions of the dyes were made in sterile test-tubes, using acid urine for one series of dilutions and alkaline urine for another. Each dilution was inoculated with one loop of a twenty-four-hour

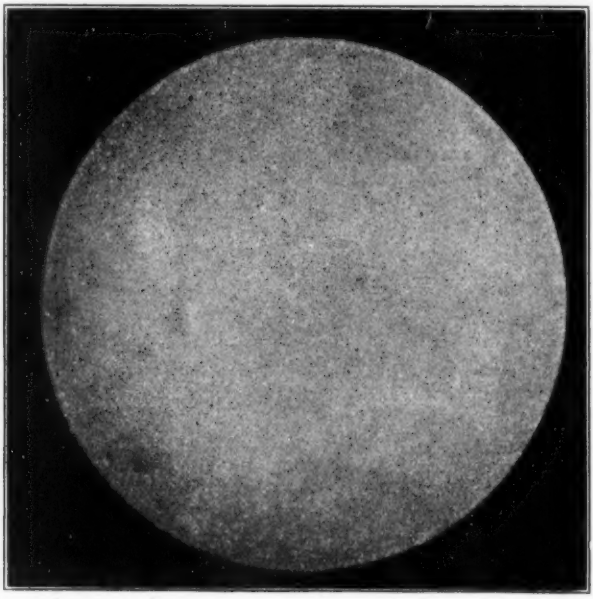


FIG. 4.—Photomicrograph (low power) of typical field in agar plate, showing absence of colonies and proving that the corresponding urine tube had contained a concentration of dye sufficient to kill the organisms during the twenty-four-hour incubation period.

broth culture of Bacillus coli in one series of experiments and with the Staphylococcus albus in another. After an incubation period of twenty-four hours (sufficient time to permit either growth or death of the organism), 0.1 c.c. was transferred from each tube to melted agar and plated. Those plates remaining sterile after incubation (Fig. 4) proved that the urine in the corresponding tubes had contained a concentration of the dye sufficient to kill the organisms within twenty-four hours. Those plates showing a few scattered colonies after incubation (Fig. 5) proved that the concentration of the dye in the urine had been sufficient to cause an arrest in the development of the organisms. This is the "bacteriostatic" action of antiseptics referred to by Hinman and should be

sufficient to control urinary infection provided the administration of the drug is continued. Finally, plates in which countless numbers of colonies developed (designated in the tables by the infinity sign ∞) proved that the concentration of the drug had been insufficient to prevent growth of the organism (Fig. 6).

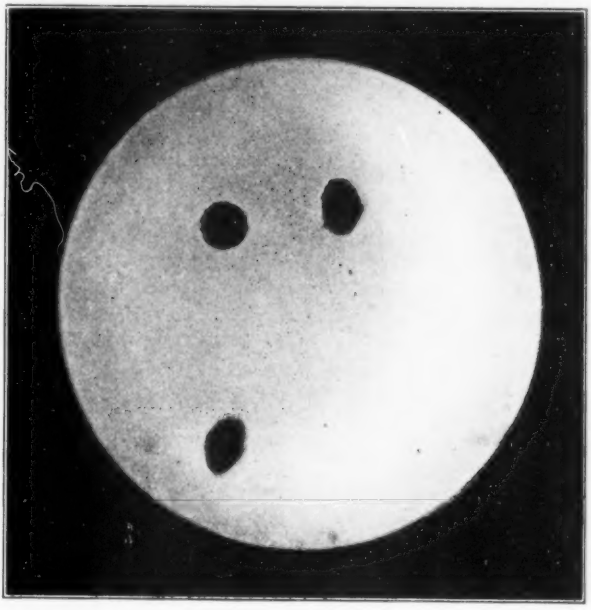


FIG. 5.—Photomicrograph (low power) of typical field in agar plate, showing a few scattered colonies and proving that the corresponding urine tube had contained an inhibitory or bacteriostatic concentration of the dye.

A consideration of Table II permits of several general conclusions. In keeping with the well-recognized clinical frequency of colon bacillus urinary infections, and with the stubbornness of such infections, is the hardiness which this organism displays in urine *in vitro* in spite of the presence of antiseptic dyes. Out of a total of 204 dyes studied only 24 prevented the growth of the colon bacillus in urine in a dilution of 1 to 1000. Of these several were effective in alkaline urine only. A 1 to 1000 solution is a relatively high concentration, considering the extreme dilutions (several greater than 1 to 1,000,000) at which these same dyes are effective against staphylococci in the same media at the same reaction Table II further shows that it is the general rule that these dyes are antiseptic in higher dilution in alkaline than acid urine. This fact might well prove to be of clinical importance, since the artificial production and maintenance of an alkaline urine is a relatively simple matter.

TABLE I.—RESULTS OF PRELIMINARY TESTS ON AGAR OF ANTISEPTIC VALUE OF THE ENTIRE LIST OF DYES AGAINST COLON BACILLUS (C), STAPHYLOCOCCUS ALBUS (Al) AND STAPHYLOCOCCUS AUREUS (Au). ALL DILUTIONS ARE 1 TO 1000. ○ = GROWTH. − = NO GROWTH.

Name.	No.	Antiseptic strength.			Name.	No.	Antiseptic strength.		
		C.	Al.	Au.			C.	Al.	Au.
NITROSO.									
Naphtholgreen B	4*	○	○	○					
NITRO					NITRO.				
Martius yellow	6	−	−	−	Naphthol yellow S	7	○	○	○
STILBEN.									
Golden yellow	9	○	○	○					
PYRAZOLON.					PYRAZOLON.				
Flavazin L	19	○	○	○	Tartrazin	23	○	○	○
Flavazin S	20	○	○	○					
AZO (MONOAZO).					AZO (MONOAZO).				
Chrysoidin Y	33	○	−	−	Erika B extra	121	○	○	○
Chrysoidin R	34	○	−	−	Erika G extra	122	○	○	○
Soudan I	36	○	○	○	Victoria yel. O	134a	○	○	○
Ponceau 4 GB	37	○	○	○	Metanil yel. extra	134b	○	−	−
Orange G	38	○	○	○	Fast yellow	137	○	○	○
Chromotrope 2R	40	○	○	○	Brilliant yel. S.	142	○	○	○
Orange III	47	○	○	○	Chrysoin	143	○	○	−
Orseillier Mixt.	53	○	○	○	Orange I	144	○	○	○
Chrysoidin	69	○	○	○	Orange II	145	○	○	○
Brilliant orange O	70	○	○	○	Azofuchsin	146	○	○	○
Brilliant orange R	79a	○	○	○	Fast yellow	149	○	○	○
Brilliant orange R	79b	○	○	○	Orange T	151	○	○	○
Palatine scarlet A	81	○	○	○	Naphthyl amino br.	160	○	○	○
Ponceau R	82	○	○	○	Azo rubin	163	○	○	○
Ponceau 3R	83a	○	○	○	Fast red	160	○	○	○
Ponceau 3R	83b	○	○	○	Fast red D	168	○	○	○
Azoeosin G	94a	○	○	○	Cochenille red A	169	○	○	○
Azoeosin	94b	○	○	○	Fast brown 3B	172	○	○	○
Fast red	112	○	○	○					
AZO (DIAZO).					AZO (DIAZO)				
Resorcin brown	211	○	○	○	Vesuvin B	284	○	○	○
Fast brown G	212	○	○	○	Azoalazarin Bord. W.	291	○	−	−
Fast brown	213	○	○	○	Brilliant yellow	303	○	○	○
Blue black	215	○	○	○	Benzopurpurin 4B	363	○	○	○
Palatine black	220	○	○	○	Benzopurpurin 6B	364	○	○	○
Brilliant crocein	227	○	○	○	Rosazurin	372	○	○	○
Soudan IV	232	○	○	○	Azo blue	377	○	○	○
Fast scarlet	248	○	○	○	Dianil blue B	380	○	○	○
Crocein scarlet	249	○	○	○	Trypanblue	391	○	○	○
Crocein scar, 7B	255	○	○	○	Chrysamin R	394	○	○	○
Bismark brown	283	○	−	−	Bavarian blue	450	○	−	−
AURAMINE.					AURAMINE				
Auramine	493	−	−	−	Auramine G	494	○	−	−
TRIPHENYLMETHANE.					TRIPHENYLMETHANE.				
Malachite green	495	−	−	−	Victoria blue 4R	522	○	−	−
Brilliant green	499	−	−	−	Fuchsin S	524	○	○	○
Lt. green SF bluish	504	○	○	○	Red violet 5RS	525	○	○	○
Lt. green SF yellowish	505	○	○	○	Acid violet 4BN	527	○	−	−
Erioglaucine A	506	○	○	○	Acid violet	529	○	○	○
Fuchsin	512	○	−	−	Formyl violet S4B	530	○	○	○
Red violet 5R ex.	514	−	−	−	Methyl blue	538	○	−	−
Methyl violet B	515	−	−	−	Soluble blue	539	○	○	○
Crystal violet	516	−	−	−	Amalga green B	542	○	○	○
Methyl violet	517	−	−	−	Patent blue	543	○	○	○
Ethyl violet	518	−	−	−	Patent blue A	545	○	○	○
Methyl green	519	○	○	○	Cyanol extra	546	○	○	○
Aniline blue	521	○	○	○					

* Numbers correspond to Gustav Schultz, Farbstofftabellen, 1914 (5th edition).

TABLE I.—*Continued.*

Name.	No.	Antiseptic strength.			Name.	No.	Antiseptic strength.		
		C.	Al.	Au.			C.	Al.	Au.
DIPHENYLNAPHTHYLMETHANE.					DIPHENYLNAPHTHYLMETHANE.				
Victoria blue R	558	○	○	○	Wool green S	566	○	○	–
Victoria blue	559	○	–	–					
XANTHONE.					XANTHONE.				
Rodamine S	570	○	–	–	Eosin	587	○	○	○
Rodamine 6G extra	571	○	–	–	Methyleosin	588	○	–	–
Rodamine G extra	572	○	–	–	Eosin BN	590	○	○	○
Rodamine B	573	○	–	–	Erythrosin G	591	○	○	–
Rodamine 3G	576	○	–	–	Erythrosin	592	○	○	–
Sulphorodamine B	579	○	○	○	Phloxine P	593a	○	–	–
Fast acid violet B	580	○	○	○	Phloxine P	593b	○	○	–
Fast acid violet A2R	582	○	○	○	Phloxine	596	○	–	–
Acidrosamine	583	○	○	○	Rose bengale	597a	○	–	–
Fast acid blue	584	○	○	○	Rose bengale extra	597b	○	–	–
Chrysolin	586	○	○	–					
ACRIDINE.					ACRIDINE.				
Benzoflavine	605	○	–	–	Phosphine N	606b	○	–	–
Phosphine	606a	○	–	–	Rheonin	607	○	–	–
QUINOLINE.									
Quinoline yellow	612	○	○	○					
THIOBENZENYL.									
Thioflavine S	615a	○	○	○	Primuline	616	○	○	○
Thioflavine S	615b	○	○	○					
OXAZINE.					OXAZINE.				
Meldola's blue	649	–	–	–	Methylene blue	659	–	–	–
New blue B	650	–	–	–					
New methylene blue	651	○	–	–					
THIAZINE.									
Thiocarmine	662	○	○	○					
AZINE.					AZINE.				
Flavindulin O	668	–	–	–	Safranin MN	683b	○	–	–
Neutral red	670	○	○	○	Nigrosine	698	○	○	○
Indulin scarlet	671	○	–	–	Indulin NN	699	○	○	○
Safranin T	679	○	–	–	Indulin	700	○	○	○
Safranin OW	683a	○	–	–					
MISCELLANEOUS.					MISCELLANEOUS.				
Scarlet 6R	..	○	○	○	Pontacyl pr.	..	○	○	○
Diphenylamino orange	..	○	○	○	Congo red				
Crystal scarlet	..	○	○	○	Scarlet B	..	○	○	○
Biebrich scarlet	..	○	○	○	Pontamine brown R	..	○	○	○
Croceine 3BX	..	○	○	○	Pontamine green GX	..	○	○	○
Guinea green	..	○	○	○	Pontamine green BX	..	○	○	○
Quinone	..	–	–	–	Pontamine black EX	..	○	○	○
Pontacyl sul. blue 5RX	..	○	○	○	Pontachrome yellow	..	○	○	–
Pontacyl ponceau	..	○	○	○	Pontamine orange	..	○	○	○
Pon. sul. acid blue R	..	○	○	○	Methylene blue ZX	..	–	–	–
Pontacyl azo flavine	..	○	○	○	Safranine T extra	..	○	–	–
Pon. sul. black 2B	..	○	○	–	Pontamine yel. SX	..	○	○	○
Pon. blue black SX	..	○	○	○	Primuline	..	○	○	○
Pontamine fast red F	..	○	○	○	Fast yellow NNX	..	○	○	○
Pontamine violet N	..	○	○	○	Erioglaucine	..	○	○	○
Pontamine red B	..	○	○	○	Pontamine fast. yel.	..	○	○	○
Pontamine blue AX	..	○	○	○	Alkali blue	..	○	○	–
Pontamine sky blue 5B	..	○	○	○	Sulphogene ind. blue G	..	○	○	○
Pontamine purpur 10B	..	○	○	○	Aurine	..	○	–	–
Pontamine blue 2B	..	○	○	○	Sulphogene gr. G	..	○	○	–
Ponta. diazo bl. BH	..	○	○	○	Sulphogene or. L	..	○	○	○
Pontachrome black F	..	○	○	○	Thionol black XX	..	○	○	○
Pontachrome bl. 6BX	..	○	–	–	Sulphogene navy blue	..	○	○	○
Hydron blue G	..	○	○	○	Hydron blue R	..	○	○	○
Sulphogene Bordeau B	..	○	○	○	Sulphogene br. G	..	○	○	○
Gentian violet	..	–	–	–					
STANDARD ANTISEPTICS.					STANDARD ANTISEPTICS.				
Mercuric chloride	..	–	–	–	Silver nitrate	..	–	–	–
Phenol	..	○	○	○	Ethyl alcohol	..	○	○	○

TABLE II.—DETERMINATION OF ANTISEPTIC VALUE IN BOTH ACID AND ALKALINE URINE OF 28 DYES SELECTED BY PRELIMINARY TEST ON AGAR FROM THE ORIGINAL 204, AS SHOWN IN TABLE I.

Group.	Dye.	No.	Antiseptic strength in urine.							
			Colon bacillus.				Staphylococcus albus.			
			Acid urine (pH, 6.4).		Alkaline urine (pH, 7.6).		Acid urine (pH, 6.4).		Alkaline urine (pH, 7.6).	
			Inhibits devel. 1 to	Permits growth. 1 to	Inhibits devel. 1 to	Permits growth. 1 to	Inhibits devel. 1 to	Permits growth. 1 to	Inhibits devel. 1 to	Permits growth. 1 to
Nitro	Martius yellow	6	1,000	10,000	1,000	10,000	10,000*	....	10,000*	
Azo	Chrysoidin Y	33	1,000*	10,000	....	1,000	10,000*	....	10,000*	
	Chrysoidin R	34	1,000*	....	....	1,000	30,000	50,000	50,000*	
	Victoria yellow	134b	....	1,000	....	1,000	1,000	10,000	1,000	10,000
Auramine	Auramine	493	....	1,000	1,000*	3,000	1,000	10,000	1,000	10,000
	Auramine G	494	....	1,000	3,000	5,000	1,000	10,000	1,000	10,000
Triphenyl-methane	Mal green	495	5,000*	....	5,000*	....	900,000	1,000,000	1,000,000*	
	Brill. green	499	1,000*	....	1,000*	....	900,000	1,000,000	900,000	1,000,000
	Fuchsin	512	....	1,000	1,000*	....	100,000	300,000	100,000	300,000
	Red viol. 5R ex.	514	1,000*	....	1,000	10,000*	100,000	300,000	700,000*	
	Methyl viol. B	515	3,000	7,000	10,000*	....	1,000,000	....	1,000,000*	
	Crystal viol.	516	1,000	3,000	10,000*	....	1,000,000*	....	1,000,000*	
	Methyl viol.	517	....	1,000	5,000*	....	3,000,000*	5,000,000	9,000,000	10,000,000
	Ethyl viol.	518	....	1,000	3,000	5,000	300,000*	500,000	900,000	1,000,000
	Victoria blue	522	1,000*	....	....	1,000	10,000*	....	90,000	
Xanthone	Rhod. 6G ex.	571	....	1,000	....	1,000	30,000*	....	70,000*	90,000
	Rhod. 3G	576	....	1,000	1,000*	3,000	100,000*	300,000	100,000	300,000
	Rose beng. ex.	597b	....	1,000	....	1,000	30,000	50,000	10,000*	
Acridin	Benzoflavine	605	1,000*	....	1,000*	....	30,000*	70,000	90,000*	
	Rheonin	607	....	1,000	1,000	10,000	10,000*	....	30,000	50,000
Azine	Flavindulin	668	1,000	2,000	1,000	2,000	900,000*	1,000,000	700,000*	900,000
	Indulin scar	671	1,000*	....	1,000*	3,000	1,000	10,000	90,000*	
	Safranin T	679	....	1,000	....	1,000	10,000	30,000	500,000*	700,000
	Safranin OW	683a	....	1,000	....	1,000	10,000	30,000	10,000	70,000
	Safranin MN	683b	....	1,000	1,000*	....	10,000	30,000	100,000	300,000
Miscellaneous	Acriflavine	...	5,000	7,000	100,000	200,000	75,000	100,000	100,000	200,000
	Safranin T ex.	...	....	1,000	....	1,000	30,000*	50,000	90,000*	100,000
	Gentian violet	...	1,000*	....	2,000*	....	100,000	900,000	700,000	900,000
Standard antiseptics	Phenol	...	....	1,000	....	1,000	....	1,000	....	1,000
	Hg. bichloride	...	10,000	30,000	10,000	30,000	10,000	30,000	10,000	30,000
	Ag. nitrate	...	10,000	30,000	10,000*	....	10,000	....	10,000*	

* Indicates that plates showed a few scattered colonies, and that all the organisms were not killed, although there was distinct inhibition of development.

3. *Toxicity and Excretion.* Twenty-seven dyes were selected from Table II as seeming worthy of further study as to toxicity and excretion. Rabbits were given intravenous injections of from 5 to 25 mgm. per kilo and the urine collected at intervals and examined for the dye. Only in those cases in which the excretion was strikingly rapid and complete was an attempt at quantitative colorimetric estimation made. As shown in Table III, several dyes (malachite green, brilliant green, crystal violet, ethyl violet, victoria blue and others) were exceedingly toxic, causing convulsions and death within a few minutes. Autopsies showed a varying and bizarre selective distribution of the different dyes through the various tissues of the body. Several dyes (for instance chrysoidin R, crystal violet, rhodamin 3G, benzoflavin, indulin scarlet and others), though not fatal, were ruled out on account of hematuria or hemoglobinuria following minute dosage. Particular attention is called to the triphenylmethane group, of which many showed antiseptic properties in extreme dilution in urine. Dyes of this group, however, were also the most toxic, and those few which did not injure the rabbit failed to appear in the urine. (See Table III.)

TABLE III.—EXCRETION AND TOXICITY. RESULTS OF INTRAVENOUS INJECTIONS IN RABBITS OF DYES SHOWN IN TABLE II TO POSSESS ANTISEPTIC VALUE *IN URINE*.

Group.	Dye.	No.	Effect on animal.		Renal excretion.	
			Dose, mgm. per K.	Result.	Dose, mgm. per K.	Result.
Nitro . . .	Martius yellow	6	10	None	10	Moderate.
Azo . . .	Chrysoidin Y	33	20	None	20	Marked.
	Chrysoidin R	34	20	Hematuria	20	Moderate.
	Victoria yellow	134b	20	None	20	Moderate.
Auramine .	Auramine	493	10	None	10	Moderate.
	Auramine G	494	10	None	10	None.
Triphenyl-methane .	Malachite green	495	20	Lethal	4	None.
	Brilliant green	499	10	Lethal	4	None.
	Fuchsin	512	20	None	20	None.
	Red viol. 5R extra	514	20	Lethal	15	None.
	Methyl violet B	515	30	Anuria	20	None.
	Crystal violet	516	4	Hematuria*	4	None.
	Methyl violet	517	40	Lethal	20	None.
	Ethyl violet	518	20	Lethal	8	None.
	Victoria blue	522	8	Lethal	8	None.
Xanthone .	Rhod. 6G extra	571	20	Lethal	10	Moderate.
	Rhod. 3G	576	20	Hematuria	10	Moderate.
	Rose beng. extra	597b	20	None	20	None.
Acridin . .	Benzoflavine	605	10	Hematuria	4	Slight.
	Rheonin	607	20	None	20	None.
Azine . . .	Flavindulin	668	40	Lethal	20	Doubtful.
	Indulin scar.	671	10	Hematuria	10	Marked.
	Safranin T	679	20	None	20	Moderate.
	Safranin OW	683a	20	None	20	Marked.
	Safranin MN	683b	20	None	20	Marked.
Miscellaneous	Safranin T extra	...	30	None	20	Marked.
	Acriflavine	...	20	None	5	Marked.
	Proflavine	...	20	None	5	Marked.

* Hematuria lasted three days.

4. *Experimental Urinary Antisepsis.* Table III shows that of the total of 204 dyes studied there remained only 13 which were antiseptic in urine (*in vitro*), which were excreted by the kidney after intravenous administration and which exhibited no toxic properties following moderate dosage (about 20 mgm. per kilo). These dyes are listed in Table IV. It then remained to attempt to demonstrate antiseptic properties in the urine of rabbits following the intravenous administration of these drugs; that is, to determine whether passage through the blood stream and kidney would interfere with the antiseptic properties, and whether sufficient dosage could be safely administered to cause adequate concentration in the urine.

TABLE IV.—EXPERIMENTAL URINARY ANTISEPSIS. RESULTS OF ATTEMPTS TO CAUSE THE SECRETIONOF ANTISEPTIC URINE BY THE INTRAVENOUS ADMINISTRATION TO RABBITS OF DYES, SHOWN IN TABLES II AND III TO BE ANTISEPTIC, EXCRETED AND RELATIVELY NON-TOXIC. C = COLON BACILLUS. Al = STAPHYLOCOCCUS ALBUS. ∞ = AN INFINITE NUMBER OF COLONIES. O = NO COLONIES.

Group.	Dye.	No.	Dose. mgm. per K.	Number of colonies which developed in in agar plate containing 0.1 c.c. of urine which had previously been inoculated and incubated twenty-four hours.							
				Urine obtained just before injection.		Urine obtained 2 hours after injection.		Urine obtained 6 hours after injection.		Urine obtained 12 hours after injection.	
				C.	Al.	C.	Al.	C.	Al.	C.	Al.
Nitro . . .	Martius yellow	6	10	∞	∞	∞	∞	∞	∞	∞	∞
Azo . . .	Chrysoidin Y	33	20	∞	∞	∞	∞	∞	∞	∞	∞
	Chrysoidin R	34	20	∞	∞	∞	∞	∞	∞	∞	∞
	Victoria yellow	134b	20	∞	∞	∞	∞	∞	∞	∞	∞
Auramine .	Auramine	493	10	∞	∞	∞	∞	∞	∞	∞	∞
Xanthone. .	Rhod. 6G extra	571	10	∞	∞	∞	∞	∞	∞	∞	∞
	Rhod. 3G	576	10	∞	∞	∞	∞	∞	∞	∞	∞
Azine . . .	Flavindulin	668	20	∞	∞	∞	∞	∞	∞	∞	∞
	Indulin scar	671	4	∞	∞	∞	∞	∞	∞	∞	∞
	Safranin T	679	20	∞	∞	∞	∞	∞	∞	∞	∞
	Safranin OW	683a	20	∞	∞	∞	∞	∞	∞	∞	∞
	Safranin MN	683b	20	∞	∞	∞	∞	∞	∞	∞	∞
Miscellaneous	Safranin T extra	. .	30	∞	∞	∞	∞	∞	∞	∞	∞
	Acriflavine	. .	10	∞	∞	0	0	0	0	∞	∞
	Proflavine	. .	10	∞	∞	0	0	0	0	∞	∞

In general the method of procedure was to compare the antiseptic properties of several specimens of urine, obtained by catheterization from a given rabbit before and at intervals of from one to several hours after drug administration. The necessity for a control urine has been pointed out in a previous publication (Davis and Hain[17]),

[17] Urinary Antisepsis: The Antiseptic Properties of Normal Dog Urine, Jour. Urol., 1918, ii, 309.

which shows that normal dog and rabbit urine, for undetermined reasons, may occasionally act as an unfavorable culture medium for the colon bacillus and may even kill this organism after several hours. Each experiment was therefore accurately controlled by a specimen of urine obtained just before administration of the drug and inoculated and subjected to identically the same conditions as those specimens obtained at intervals after injection.

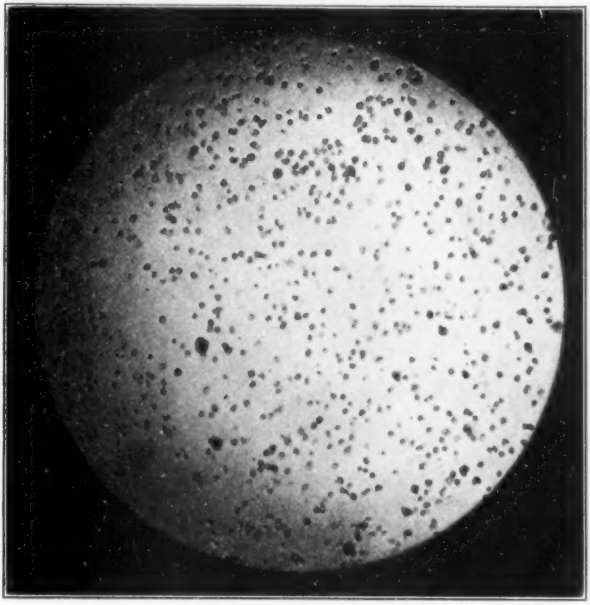


FIG. 6.—Photomicrograph (low power) of typical field in agar plate, showing a countless number of colonies and proving that the corresponding urine tube had contained an insufficient concentration of dye to prevent growth of the organism. The number of colonies in such a plate is designated in Table IV by the infinity sign ∞.

Two samples (1 c.c. each) were transferred from each specimen of urine to sterile test-tubes, inoculated with B. coli and S. albus respectively (one loop of a twenty-four-hour broth culture) and incubated twenty-four hours, after which 0.1 c.c. was transferred from each tube to melted agar and plated. This technic was identical with that described in a preceding paragraph for determining the antiseptic properties of the same dyes in voided human urine, with the exception that the dyes were not added to the urine but were excreted by the kidney. The plates were inspected after forty-eight hours. A plate showing no colonies (Fig. 4) or

very few colonies (Fig. 5) proved that particular specimen of urine to be antiseptic, while the presence of countless numbers of colonies (illustrated by Fig. 6 and designated in Table IV by the infinity sign ∞) proved that the organism had grown and developed and that the urine had acted as a favorable culture medium. This method, dependent upon observing the number of colonies in an agar plate, accurately determines whether the organism has developed or died during the incubation period and is not open to fallacy, as is the method dependent upon gross inspection of incubated urine.

Table IV summarizes the results of attempts to demonstrate antiseptic properties in rabbit urine following the intravenous administration of the 13 dyes shown by previous selection (Tables I, II and III) to be antiseptic, excreted and non-toxic in moderate dosage. The same table shows the results of similar experiments carried out with proflavine and acriflavine. As a previous publication has pointed out (Davis and White[8]), and as the above experiments verify, proflavin and acriflavin are experimentally successful in that antiseptic properties in the urine may be definitely demonstrated following intravenous administration. (The flavins giving these results were manufactured by the Boots Pure Drug Company, Nottingham, England.) Out of the entire list of 204 new dyes, however, although preliminary experiment justified the final selection of thirteen, the properties of which indicated their possible value as internal urinary antiseptics, with none excepting proflavin and acriflavin, was it possible to cause the secretion of antiseptic urine by intravenous administration. In spite of the fact that these several selected dyes approached the ideal requirements (that is were antiseptic in urine, were excreted by the kidney and were relatively non-toxic), yet they failed at the final test when passed through the blood stream and kidney.

Conclusions.—1. There is no known drug ideally suited for the purpose of internal urinary antisepsis.

2. Of a total of 204 anilin dyes investigated 61 were found to possess antiseptic properties in agar, and 28 of these were efficient as antiseptics when added to voided urine.

3. As regards selective action against various organisms, this property was exhibited by no less than 44 dyes, in every case the colon bacillus proving more resistant than the staphylococci. There were only 24 which inhibited the colon bacillus in urine in a dilution of 1 to 1000.

4. There was almost no exception to the rule that antiseptic action was exhibited in higher dilution in alkaline urine than in acid urine. Attention is therefore called to the fact that these dyes are most efficient in urine of a reaction which renders urotropin inert.

5. The azo dyes give no promise of value, since of 37 of this group studied only 3 possessed antiseptic properties, and these only to a slight degree.

6. Of the triphenylmethanes many were antiseptic in high dilution in urine (some in dilution greater than 1 to 1,000,000). Of these, however, all but one were toxic and none was excreted by the kidney. This group is, nevertheless, worthy of further investigation.

7. Of 21 dyes of the xanthane group 3 were antiseptic in voided urine, and 2 of these were excreted to a moderate degree.

8. Of 4 acridine dyes 2 were antiseptic in urine. Neither was excreted.

9. Of 9 dyes of the azine group 5 were antiseptic in urine, and 3 of these (Safranin T, Safranin OW, Safranin MN) were excreted by the kidney with great rapidity and completeness and were non-toxic in 20 mgm. per kilo dosage.

10. By a study of 204 anilin dyes, chosen at random, it has been possible to select 15 which are (*a*) antiseptic in urine, (*b*) excreted by the kidney and which are (*c*) relatively non-toxic. With only two of these, however (proflavin and acriflavin) was it possible to demonstrate the secretion of antiseptic urine following intravenous administration.[8]

11. Considering that rapid renal elimination of anilin dyes is not unusual; that there are not a few dyes, relatively non-toxic, which exert a bacteriostatic action when diluted to infinitesimal amounts in voided urine; and that out of 204 dyes it has been possible to select 15 which approach the ideal and 2 which are experimentally effective; it is within reasonable expectation that a dye clinically suited for use as an internal urinary antiseptic may be discovered or synthesized. Experiments to date indicate that dyes of the triphenylmethane, xanthone, acridin and azin groups (particularly) the latter) give more promise of value.

THE FOURTH VENEREAL DISEASE, ULCERATIVE AND GANGRENOUS BALANOPOSTHITIS: WITH CASE REPORT.

By William M. Donovan, M.D.,

INSTRUCTOR IN CLINICAL MEDICINE, UNIVERSITY OF WISCONSIN MEDICAL SCHOOL, MADISON, WIS.

Judging by the dearth of case reports and the rare mention of the so-called "Fourth Venereal Disease," it would seem that the existence of this condition is not a matter of common knowledge among physicians. Since Corbus and Harris[1] first called it to the attention of the profession in this country in 1909 but two others have made case reports in the American journals.[2] [3] Some of the

[1] Jour. Am. Med. Assn., May 8, 1909, lii, 1474.
[2] Bond, S. P.: Urol. and Cut. Rev., 1919, xxiii, 211.
[3] Ross, C. F.: Virginia Med. Monthly, xlv, 36.

current text-books on urology make no mention of it while others merely give it passing notice. The article by Corbus in Cabot's recent treatise on *Urology* is quite complete, and by far the best that the author has encountered.

Frequency.—Were the disease extremely infrequent this lack of appreciation would be of no moment, but Bataille and Berdal,[4] reporting 120 cases, state that it comprises from 2 to 3 per cent. of cases seen at l'hôpital du Midi. Sherber and Müller[5] report 50 cases from Vienna seen in less than one year. Corbus[6] says that it occurs infrequently in private practice—once in 200 cases—but is much more frequent in the clinics. He reports 7 cases in two contributions.

Definition.—The "Fourth Venereal Disease," or specific ulcerative and gangrenous balanoposthitis, is an acute inflammatory disease of the glans penis and opposed surface of the prepuce, characterized clinically by ulcerations and at times gangrene, accompanied by a copious flow of strongly odorous pus and caused by a spirochete in association with a fusiform bacillus. Constitutional symptoms are at times present.

History.—Previous to the work of Bataille and Berdal (1889–1891) several forms of balanoposthitis were recognized, including the ordinary form due to dirt, smegma, phimosis, etc., and some special forms, as the diabetic in which yeasts were found by Simon[7] and the gonorrheal forms.

Ulceration and gangrene had been noted in cases of balanitis before this time but were not considered to constitute a disease entity.

Bataille and Berdal were the first to recognize in this condition a separate disease and to demonstrate its infectious, venereal, inoculable and auto-inoculable nature, and to describe its clinical aspects and etiology. They named it "Balanoposthite erosive circinée."

To demonstrate its inoculable nature they used humans, infecting them with pus from typical cases as follows:

(*a*) Pus was touched to a small incision on glans made by a scalpel.

(*b*) Pus was applied to the glans and prepuce after rough rubbing with a small stick.

(*c*) The inner surface of the prepuce was rubbed onto an ulcer of a case of this disease.

The results were positive in all three types of experiments. The disease was proved auto-inoculable by touching a freshly abraded spot on the glans or opposed preputial surface with pus from the same individual and securing the development of a new ulcer—thus

[4] Mod. Med., 1891, ii, 340, 380, 400, 413.
[5] Arch. f. Dermat. u. Syph., 1905, lxxvii, 77.
[6] Erós. and Gang. Balanitis, Jour. Am. Med. Assn., 1913, lx, 1769–1774.
[7] Internat. Cong. Med., London, 1881.

simulating chancroid. There were no "takes" when these same tests were applied to the urethra or any surface other than that lining the preputial sac.

Etiology.—Bataille and Berdal ascribed the etiology to a spirochete which they found in nearly all cases, indistinguishable from that found in Vincent's angina, noma and mercurial stomatitis. No mention was made of the fusiform bacillus. Sherber and Müller[5] and Corbus and Harris[1] not only found a similar spirochete but also a fusiform bacillus to a symbiosis of which they attributed the disease. The former writers were able to cultivate the bacillus, and in their first communication emphasized its importance over the spirochete. In a later paper (quoted from Corbus[6]), having failed to produce the disease by inoculation with this bacillus, they came to the conclusion that the spirochete plays the essential role in the etiology.

However, it may be that the bacillus and spirochete represent different morphologic types of the same organism, as seems to be the consensus of opinion regarding those found in Vincent's angina.

The vibrio is anaërobic, Gram-positive, 2 μ long by 8 μ wide, with pointed ends. It can be cultivated on serum agar.

The spirochete also is anaërobic, Gram-negative, 6 to 30 μ long by 2 μ wide. Its curves are not acute and its motility is great as observed in the dark field. The ends terminate in the center of the spiral.

As predisposing causes may be mentioned:

1. Redundant prepuce with a tendency to phimosis—favorable to anaërobic conditions.

2. Unclean preputial sac with its decomposing smegma.

According to Corbus[6] unnatural sexual relations, or wetting the labia with saliva, is a predisposing cause, it having occurred in all of his cases. Opposed to this, however, is its absence or extreme rarity among high school boys in the masturbating age; the statement of Bataille and Berdal[4] that women and women alone can give it, and the fact that Sherber and Müller[5] do not mention it, at least in their first paper. It has still to be proved, too, that the organisms here are identical with those of Vincent's angina or the ordinary mouth spirochetes, although they are morphologically indistinguishable.

Pathology.—There are two forms of the disease, the ulcerative and the gangrenous, the latter being simply an advanced stage of the former.

Ulcerative Form. Exfoliation of epithelium occurs in numerous spots on the surface lining the preputial sac and preputial meatus. Progression leads to ulcerations which are irregular in outline, of a somewhat punched-out appearance, bright red in color, with a whitish margin of necrosed epithelium. Later the ulcerations become quite deep and are covered by a grayish-white mem-

brane which discharges much pus of a characteristic foul odor and yellowish-white appearance.

Microscopically there is infiltration by leukocytes, injection of vessels and exudation of serum. The spirochetes and fusiform bacilli penetrate the tissues even to the lumen of the bloodvessels and neighboring lymph nodes (Sherber and Müller).[5]

Gangrenous Form. Here the process continues to the stage of mortification, sometimes affecting the whole penis and necessitating amputation.

Symptomatology.—The period of incubation ranges from two to eight days. Subjectively, at first, there is mild itching, followed later by constant burning pain in the preputial sac, and extreme tenderness of the penis to manipulation. Pain on urination is characteristically absent at first, and when present later is due to urine in the preputial sac bathing the ulcers.

Objectively at first one sees the exfoliations followed soon by ulcerations and pus, etc., as described under pathology, the favorite sites being the sulcus, prepuce and glans in the order named. Edema of the whole penis, phimosis with heat and redness and palpable dorsal lymph vessel are common. Bilateral inguinal adenitis of an indurative character is frequent, but the nodes do not suppurate nor cause much discomfort.

Constitutional symptoms are absent in the mild cases, but prostration, fever, vomiting, etc., come on in more advanced ones.

The course of the disease is progressive to gangrene in cases with marked phimosis unless proper treatment is instituted, but may subside spontaneously when there is no such phimosis if the patient employs the ordinary methods of cleanliness. With proper care the cases are usually cured in two or three weeks.

The disease is sometimes complicated by the simultaneous presence of syphilis.

Diagnosis.—This is finally clinched by finding the characteristic vibrio and spirochete in the pus. While spirochetes are frequently found in the normal preputial sac, sometimes morphologically identical with those under discussion, the vibro is never present (Sherber and Müller)[5] and the combination of the two is pathognomonic.

Differentiation is to be made from chancroid, chancre, gonorrhea, herpes preputialis, veneroid ulcer and ordinary balanitis. From a consideration of the known facts and characteristics of these diseases, together with microscopic examination, which after all is the means, *par excellence*, the diagnosis is easy.

Treatment.—Prophylactically, circumcision is of the greatest importance, since the organisms are anaërobic.

Cauterization, which might first come to mind, is contra-indicated not only because of the pain occasioned but also in that it renders anaërobic conditions possible beneath the coagulated albumin. The positive indications are to:

1. Treat the phimosis by a dorsal slit, thus aiding in the application of remedies and favoring aërobic conditions.

2. Irrigate the sac every few hours with peroxide of hydrogen solution.

3. Apply arsphenamin or neoarsphenamin daily to the ulcers in powdered form.

The following case, recently seen by me in consultation with Dr. George Fahr, illustrates a typical example except that the ulcers were confined to the prepuce.

Case History.—A. B., a white male, aged twenty-six years, a University student, presented himself at the University clinic giving the history that eight days previously he had intercourse with a prostitute. Six days later he noticed itching and burning in the preputial sac, which was followed next day by a copious yellowish-white discharge of pus and much tenderness and swelling of the penis. There was no pain on urination. On examination the penis was red, tender and swollen and had a palpable dorsal lymph cord. There was a foul-smelling discharge of pus which on microscopic examination revealed the typical spirochetes and fusiform bacilli of this disease. Phimosis was present. Pain on manipulation of the part was severe. On clearing away the pus small ulcers were visible on the preputial meatus and the internal aspect of the prepuce. The glans was red but not ulcerated. The inguinal nodes were palpable, indurated and slightly tender.

The ulcers gradually deepened, new ones formed and some coalesced. Under a plan of treatment somewhat similar to that advocated in the body of this article there was complete recovery in less than three weeks. Unnatural intercourse was denied in this case.

AMNESIA AFTER CHILDBIRTH.

By Charles W. Burr, M.D.,

Professor of Mental Diseases in the University of Pennsylvania.

In the first case, childbirth was the exciting cause of dementia with amnesia, in a woman strongly predisposed to insanity. The second illustrates a similar amnesia, resulting from an incidental complicating encephalitis occurring during pregnancy, in a woman free from pathological predisposition. In all other regards (the personality of the patients, their inheritances, the exciting cause of illness, and the accompanying symptoms) the two cases are unlike.

Case I.—The patient's father was a man of unusual mental brilliancy, who, starting life with only a grammar-school education

and entirely without social influence, became not only wealthy, but, and this is more important, in judging mentality, a person whose opinions carried weight and who was respected in his community. He began when about thirty years old to drink heavily, not socially but secretly. In his earlier life he did not crave alcohol and drank rarely and moderately, yet he died a confirmed alcoholic, in his forty-fifth year, from cardio-vascular-renal disease. He was therefore not an accidental drunkard, made such by environment, but a man with congenitally tainted protoplasm, protoplasm having a pathologic affinity for alcohol. The patient's mother was very neurotic, given to outbursts of anger, hard to live with, unreasonable and always on the edge of insanity. She died at the age of thirty from some acute infection. She had several phantom pregnancies and three children, the first of whom died at birth, the second is a selfish, frivolous and not very intelligent young woman, and the third the subject of this report.

The patient was always "peculiar," but fond of music and outdoor life. She reached the second grade of a country high school at fifteen years, and then, being self-willed and under little control, informed her people she would not go to school any longer; she did not. As a child she never slept alone because of terrifying dreams, was bad-tempered, difficult, indeed impossible to train in self-control, but never physically ill. Menstruation began at fifteen years. (Probably mental unbalance, so frequent at puberty, was the real cause of her stopping school.) During adolescence she formed several transitory but violent attachments to boys, and by the time she was eighteen her sexual tendencies caused the wiser of the young men of her social circle, who were looking for wives, to avoid her. She married at twenty-two a foolish and infatuated youth, by whom she has had three children (all still living) in four years. Even before her attack of definite mental illness she was, though not a nymphomaniac, pathologically strongly sexed, entirely selfish, somewhat lacking in moral sense and with little intelligence.

In May, 1919, four weeks after the birth of her last child, who is claimed to be in good physical health, she suddenly became delusional, violent, suspicious of her husband, believed Christ was about to come again, masturbated frequently and slept but little. Six weeks after the onset of her illness, being left alone for a few minutes, she ran away and a few hours later was picked up in the street by the police, confused, erotic and exhibiting herself. She was taken to a hospital in a state of "acute mania," which lasted some days, after which she grew quieter but developed the delusion that she was the mother of Christ and at the same time stated she was going to marry a childhood friend whom she had not seen or heard of for years. (It is noteworthy that she had never received any religious training and never passed through any of the religious experiences common to adolescents, though in her father's family her forebears

had been strictly orthodox in belief and conduct.) Her husband, whom she still recognized, she accused of infidelity and would have nothing to do with. She was talkative, playful, impulsive, noisy, shameless, dirty and destructive. Very early in her illness she began to have recurring transitory visual and auditory hallucinations concerning religious and sexual matters, and throughout its course she wrote long, incoherent, obscene, profane and erotic letters. She gradually became quieter and after some months ate and slept well, was clean in her person, and, for the most part, quiet in her talk, though the erotic element still existed, because whenever she got even a glimpse of a man, no matter what his age, appearance, dress or race, she would call out to him and behave shamelessly. She masturbated much less frequently. Most of the time, except during the first months of her illness, she was emotionally apathetic, the sexual excitement being episodic, though even to the end she had occasional outbursts of apparently causeless anger.

The most interesting symptom was loss of memory or rather power of recollection. This loss especially concerned persons. She did not recognize her husband, treated him as she did all other men, but had no realization that she had ever seen him before. A relative who had taken care of her from infancy she did not recognize. Even seeing her children caused no emotional response and failed to awaken remembrance of them. For months she did not know where she was, and, though told repeatedly, always forgot in a few minutes. She retained ability to read and write throughout her illness, remembered the name of her home town, the place where she had lived as a girl and the memory loss involved not only events which had happened since her pregnancy; most of the incidents of her whole previous life were blotted out. For a long time also she had no idea of the passage of time; this really was the result of the memory loss; having no remembrance of what happened and was happening, she had no measure of time. During part of her illness she paid no attention to events happening around her: sometimes she was too maniacal, at others too apathetic, to do so. This period has remained a blank in her life. It really was not a memory loss, for memory is the permanent impress of stimuli upon the nerve cells and her nerve cells, for a reason unknown to us, refused to receive impressions. Mere lack of attention does not explain it because, as is well known, things we pay no attention to at the time may make their impress and be recollected long after.

For many months she responded normally only to the primitive instincts of hunger and sex, the latter being greatly exaggerated. When she had recovered enough to answer with verbal correctness when asked if she were married, she did not really understand what marriage connoted and did not think it strange she never saw her husband. She did not recognize him on the rare occasions when he was allowed to call on her and was not depressed by her separation

from her children. She never spoke of them. During this period she had no intellectual life, never carried on a train of thought save when asked a question, was purely a creature of impulse, without power of inhibition, and had no continuing self-consciousness. She lived from moment to moment, without remembrance of the past or thought of the future. While she was under my care she showed no physical signs of disease except a pathologic growth of hair; some previously fine hairs on the chin and upper lip became coarse and marked. A few very coarse hairs also appeared on the cheeks in front of the ears. She presented no other visible evidence of endocrine gland dysfunction.

Convalescence was slow and the first real sign of improvement was the cessation of sexual excitement. (Though the religious delusions had passed away sometime before, they had been followed by so many other symptoms that their fading out was no indication of returning health.) Next she began to realize her loss of memory, at first without any emotional reaction, but later comprehending that she must be ill and worrying, though only slightly, about it. Power of recollection was one of the last functions to return, but the last of all, and it never has really returned, was affection for her husband and children. She even today has no affection, but merely animal feeling. After she recovered enough to understand intellectually what the words marriage and motherhood meant, she was still without the slightest affection for either husband or children. This lack of feeling toward her husband was not caused by her delusion of his infidelity (it had passed out of her mind long before) and persisted for many weeks after the entire period of her acute illness had become a blank in her life. Now, about thirteen months after the onset of her illness, she is able to live at home and to take nominal, not actual, charge of the house. Though to the careless observer she would seem to be a normal woman of a rather low mental type, she is, as a matter of fact, somewhat demented, as is shown by her indifference to her husband and children and her childish outlook on life. A large part of the time of her illness is a blank to her, though the power of recollecting events in her earlier life and incidents which occurred during her convalescence has largely returned. The amnestic period has not, however, clear-cut boundaries.

Case II resembles the first in that amnesia was the great symptom. It is unlike in its cause (encephalitis) in the presence of a marked motor ataxia in both legs for many months, the absence of sexual symptoms, and in the patient's excellent ancestry, which gave her a protoplasm congenitally wholly normal. Her parents and grandparents, uncles and aunts were all, as I know from my personal knowledge, healthy mentally and physically. The patient's first pregnancy, which occurred in her twenty-sixth year, passed un-

eventfully; the child was normal at birth and remains so now, five years later. The second pregnancy occurred when she was twenty-eight years old; the child, a girl, was, I am told, physically healthy at birth, and so remains. During this pregnancy the mother had very severe morning vomiting, and just before the birth was seized with an illness which was diagnosed meningitis by the attending physician. She rapidly became palsied in both legs, and lost sight, speech and hearing. I suspect the alleged loss of sight was really photophobia and that the meningitis was really encephalitis (the cerebral type of infantile spinal palsy). She became delirious at the child's birth, and a week or ten days later, when the delirium cleared, recollection of past events was lost, not to be regained, even partially, for more than three years. When I saw her two years after the onset ataxia was so great in the legs she could neither stand nor walk, but there was no palsy; on the contrary, she could move the legs in bed strongly and with precision of movement. Striking the left patellar tendon caused adduction of the thigh, but no extensor movement of the leg, and striking the right caused adduction of both thighs. There was no ankle clonus and no plantar reflex. Sensibility to touch, pain and temperature was normal everywhere. There was marked general emaciation but no local trophic wasting, and no changes in the electric reactions of the muscles. Speech and swallowing were normal. The heart was normal, but the blood-pressure was only 100–70. There was a little incoördination in the left arm, but otherwise both arms were normal.

In addition to emotional indifference, and a loss of all sense of responsibility, the most marked mental symptom she presented, and her family told me it appeared immediately after the transitory delirium at the onset of her illness, was amnesia for events in her past life. She did not recognize any of her family, had no recollection of ever having been married or having born children (the second was born at the commencement of her illness), she did not know where she had lived, where she had gone to school, or what her previous life had been. On the other hand she retained her vocabulary, knew the meaning of words and talked sensibly. Her handwriting retained its former features. She remembered much of what she had learned at school, but almost none of the events of her school life, the friends she had made, and the like. She remembered how to sew. She had no delusions and her sense of sexual morality was strong, or rather it would be more accurate to say that she had no sexual feeling. Her manners were ladylike and her talk always clean. She (when under my care and for months previously) knew that there is such a thing as memory and that she had lost the faculty. At first she took this and her curious state of being the wife of a man whom she did not know with entire emotional apathy. Later it worried her greatly. She had no power of fixing anything in her memory. For example, if she started to read an article one

column long, in a paper, she would forget the first paragraph entirely before she reached the last. Things told or seen also made no impression. She conversed intelligently with me daily for months, and yet each day I was a new face, an unknown person. Later she almost suddenly regained the power of retaining and of recalling visual and auditory and indeed all stimuli. She then, of course, after once (in her new and normal state) seeing me, remembered me.

Almost three years after the onset she slowly regained ability to walk well. She has not as yet regained the power to recollect her past life save in a vague way, and one period is blotted out. Her natural feelings for her husband have returned, but whether it be a case of refalling in love or the return of an old love, who can tell? She does not remember her courtship and marriage nor the birth of her children. She recognized and remembered her mother and sister before she recalled her husband. She is now actually, not nominally, in charge of her home and has no dementia. Her judgment is good, and she behaves like a wise mother to her children.

Study of these two women reveals several interesting things. They illustrate the influence of heredity for good and evil. The first had a bad family history, was never really normal, and needed only the slightly added stress of several pregnancies in rapid succession to break entirely; the second, of good heredity, did not break from the stress of pregnancy but required a complicating infection (encephalitis) directly invading the brain, and, though amnesic, was not insane. Throughout her illness she retained what the insane, save the simple melancholiacs who are in a class by themselves, always lose, the moral sense.

Though we speak of the insanity of the puerperium there is no mental symptom or group of symptoms pathognomonic of pregnancy or childbirth, and almost every type of insanity may occur in association with childbearing. Even paresis, which is the one insanity having one cause and one only, syphilis, may have as its immediate occasion for appearing, pregnancy or more often, the act of birth. Childbirth almost always lights up a latent malaria, which sometimes is accompanied by a violent malarial delirium. Uterine sepsis also causes a delirium similar to that caused by fever from any cause. The most common true mental disease is a very acute confusional state.

Amnesia, except as a part of dementia, is rare and never occurs as an isolated symptom. Memory and recollection are not synonymous. Memory is passive—the permanent effect of a stimulus upon a cell. It is the unconscious storing of impressions in cells. Recollection is active: is the bringing anew into consciousness of the sensation, emotion or intellectual act caused by the original stimuli. Cells which have nothing to do with consciousness may be stored with memories and cells which have to do with consciousness may

also store memories which, though necessary to life, have no relation with consciousness. Again, certain memories must, at one stage of life, be recollected, be brought into consciousness, before a given act can be performed, while later all that need consciously be done is to will the act. For example a child learning to write must bring into the very center of consciousness the recollection of the muscular contractions needed to make each letter, while the ready penman is entirely unconscious of his muscular movements in writing: he simply orders the nerve-muscular apparatus to write, and it does so unconsciously. The same thing is true of walking, playing musical instruments and a thousand other acts. Probably every cell in the nervous system, if not every cell in the entire human organism, and indeed in all animal organisms, which performs any active function, is the seat of memories that though useful to life are never recollected, never come into consciousness. Muscle cells surely improve their function by practice, the result of unconscious memory. So do the cells having intellectual functions, and it is probable, certainly more than hypothetical, that all cells which secrete do the same. A few cells store no memories because they need none, having no active function, being mere bricks in the edifice, *e. g.*, those of bone, the crystalline lens and the outer layer of the epidermis.

Memory and recollection may be defective in several ways: I. Total permanent amnesia, *i. e.*, a complete and lasting loss of memory and power of recollection of all experiences. II. Partial amnesia, *i. e.*, loss of memory for a certain class of things, *e. g.*, amnestic aphasia and amnestic amusia (the loss of memory of the movements needed to be made to play a musical instrument). They are accompanied by word and music deafness. III. Amnesia covering only the events happening during a limited period of time, *e. g.*, just before an accident, before and after an epileptic fit or a period of delirium. IV. The amnesia accompanying alternating (double) personality, in which the patient at one time is one personality at another another, neither personality having knowledge or memory of the other. Though there are undoubtedly genuine cases of double personality, it is often pretended to be present by imaginative and histrionic ladies and gentlemen whose sense of fun, if not some more serious motive, leads them to hoodwink innocent and confiding gentlemen of science who, passing their lives in examining that always truthful witness, Nature, totally lack the useful scepticism of members of the defective force, and is today, since the condition is widely known, used by criminals of the higher class, who having disappeared and then been found, wish to give a good reason for their disappearance.

Total permanent amnesia, in the strict meaning of the word, never occurs save in the very last stages of dementia. The nearest approach to it is seen in paresis and senile dementia, but even in them some memories and some power of recollection are retained

until almost the last. The bed-ridden paretic, too demented to be delusional, showing no evidence of thinking, may yet prove by his behavior at eating time that he has a memory of certain favorite foods.

III is the type of amnesia most frequent after childbirth. Type I occurs in greater or less degree when a confusional state passes on to permanent dementia. II (amnestic aphasia) follows when a cerebral thrombosis involving the sensory speech centers occurs. It also may be transitory, in which case it probably is the result of local cortical poisoning.

Cases similar to those here reported are rare, but what percentage of pregnancies are followed by mental disorder remains unknown, because the published statistics are based on small series and on hospital cases only. For obvious reasons the women who go to maternity hospitals are more prone to complications than are those who are treated at home. The former, as a rule, have a poorer heredity and have had all their lives a poorer environment. Hence, hospital practice gives too high and private practice too low a percentage of mental disorders. The important element in prognosis as to future mental health in any pregnant woman, barring an accidental infection (such as Case II suffered), is her heredity.

REVIEWS

TREATMENT OF GONORRHEA. By NORMAN LUMB, O.B.E., Clinical Assistant to St. Peter's Hospital, London. Second edition. Pp. 120. Philadelphia: Lee & Febiger, 1920.

As a manual whose purpose it is to give to the general practitioner assuming charge of a "treatment center" (in England) a concise *resume* of this disease and its modern treatment this little book should meet a demand. It is of interest to find the author's faith and confidence in vaccine therapy, so little used in America, a method he employs routinely from the onset of the attack, and sustains its value from large army experience. We will not follow him, however, when he advises complete urethral lavage into the bladder in the beginning anterior urethritis—a method prone to spread infection that cannot appeal to any logical mind and a risk the author himself cautions against a few pages farther over. This is the only criticisable point found and is largely out-weighed by many commendable features that properly endeavor to lift the treatment of this communicable disease out of the rut of quackery and therapeutic desuetude on to a plane of scientific therapy.

A. R.

PUBLIC HEALTH AND HYGIENE. IN CONTRIBUTIONS BY EMINENT AUTHORITIES. Edited by WILLIAM HALLOCK PARK, M.D., Professor of Bacteriology and Hygiene in the University and Bellevue Hospital Medical College, and Director of the Bureau of Laboratories, Department of Health, New York City. Pp. 884; 123 illustrations. Philadelphia: Lea & Febiger, 1920.

BECAUSE of the great advances made in public health and hygiene in the past few years, this book comes at an opportune time. It contains much information of recent development. In this broad field no one individual could be proficient in all the ramifications of the subject, so very wisely the book is composed of a number of essays by writers who have had unusual experience in special branches. All has been collected under the editorial supervision of Dr. Park, who has himself written five chapters and one in collaboration on bacteriology and serology. The chapter on the prevention of infectious diseases is extremely valuable, because of the sugges-

tions for the control of the contagious, infectious and parasitic diseases. The knowledge obtained in the recent epidemics of pneumonia and influenza are presented here. The technic and application of the Schick test are given in a most practical way. Epidemiology is admirably outlined by Soper. Dodd discusses sanitary surveys. Winslow sets forth the needs and means of ventilation. Veiller writes interestingly on housing. Guerard elaborates on housing and plumbing as well as on soil and additional points on personal hygiene, while Fisk goes into the question of personal hygiene. Dunham discusses food and Atkinson the preservation and adulteration of food. Hess tells about vitamines. Bowles devotes a chapter each to water supplies and their purification and sewage and waste disposal. Mannheimer gives sanitation of swimming pools. Berry, military hygiene. Connor, tropical hygiene. Harris, individual hygiene. Baker, child hygiene. Bolduan discusses the sociologic and economic aspects of disease and public health education. Hoch, mental hygiene. Goddard, mental defectives. Cofer, maritime quarantine. Guilfoy and Wynne, vital statistics. Overton, rural public health work. The book should be well received by the medical profession and public health workers because of its thoroughness. A. E. S.

Outlines of Internal Medicine for the Use of Nurses and Junior Medical Students. By Clifford Bailey Farr, A.M., M.D. Professor of Gastro-enterology, Graduate School of Medicine and Associate in Medicine, Medical Department, University of Pennsylvania; Visiting Physician, Philadelphia Hospital for Contagious Diseases; Assistant Visiting Physician, Philadelphia General Hospital. Third and revised edition. Pp. 406; 70 engravings and 6 plates. Philadelphia and New York: Lea & Febiger, 1920.

The third edition of this well-known member of "The Nurses Text-book Series" presents the same plan of subject treatment to be found in the preceding edition. Of the ten parts constituting the whole volume, eight are devoted to diseases of the various systems and two to harmful agencies (physical, chemical, bacterial), invading the body from without. The book is planned to supply the basis for a nurse's course in medicine and in addition to serve as a work of reference to which the nurse may turn for information.

It is a big question as to how much medicine should be taught to nurses in training. Undoubtedly an insufficient amount of information is dangerous. It would seem that the author of this work has incorporated just enough to make for adequately trained caretakers of the sick. Generally the medical courses offered to nurses have been of a desultory character.

Little exception can be taken to the information contained in the lines of this edition, inasmuch as it only touches on the fundamental and well-known principles of medicine. This is, of course, as it should be. The arrangement is well done and the index is sufficiently full for a reference work. T. G. S.

THE NEW PHYSIOLOGY IN SURGICAL AND GENERAL PRACTICE. By A. RENDLE SHORT, M.D., B.S., B.SC. (LOND.), F. R. C. S. (ENG.), Examiner in Physiology for the F.R.C.S.; late Hunterian Professor, Royal College of Surgeons; Senior Assistant Surgeon, Bristol Royal Infirmary; Lecturer on Physiology, University of Bristol. Fourth edition. Pp. 291. New York: William Wood & Co., 1920.

IN 1911 the first edition of *The New Physiology in Medical and Surgical Practice* appeared. It evidently filled a need, for it has been reprinted several times and has now reached the fourth edition. The title is somewhat circumscribed and one must ask when *the* new physiology begins. In the opinion of the reviewer *the* could well be omitted. According to the author's statement in the first preface, "Many of the discoveries of the past ten years which have so changed the face of physiology are fraught with vast possibilities for the clinician;" while in this fourth edition he says that he has gathered the results of study, observation and experiment conducted during the last five years by Americans in research in pure physiology and British investigators devoting themselves especially to problems arising out of the material presented by the war. Therefore we interpret *new* to refer to the last two decades. The author attempts to sift out from this new physiology that which is likely to be of value in the actual diagnosis and treatment of patients.

Dr. Short has succeeded in presenting a most interesting and readable book with topics arranged by chapters in the following sequence: Food deficiency diseases; researches on blood, the heart, surgical shock; recent work on the functions of the stomach and intestines, the genital glands, the growth of bone, the thyroid and parathyroid glands, the pituitary and pineal glands, oxaluria, immediate and remote poisoning by chloroform, the functions of the spinal cord and peripheral nerves; localization of function in the brain; the action of cutaneous anesthetics and an appendix on the absorption of nitrogen from the amino-acids. At the close of each chapter abundant references give satisfactory suggestions for further reading, and an adequate index is among the valuable assets of the book.

There is sometimes disappointment in the lack of practical applica-

tion of results of experiments; perhaps this application of latent ideas is not too much to expect of the reader who is supposed to be "a general practitioner, consulting surgeon" or "candidate for the higher examinations in physiology." The absence of illustrations is noticeable and hardly compensated by a somewhat spectacular frontispiece. Undoubtedly frequent illustrations would be illuminating to those readers whom Dr. Short designates in the preface as "having the most elementary knowledge of physiology" and in consideration of whom "all technical terms have been avoided or defined."

DIABETES. By PHILIP HOROWITZ, M.D. Pp. 196; 27 illustrations; 2 plates. New York: Paul B. Hoeber, 1920.

DR. HOROWITZ has brought forth a little book on diabetes which has for its purpose the thorough correlation of the treatment between the patient and the doctor. The advice that he gives is sensible and practical and will give the patient a clear conception of the proper treatment of his condition, and give at the same time to the doctor a firm foundation upon which to base his treatment.

J. H. M., JR.

THE MEDICAL CLINICS OF NORTH AMERICA. Volume IV; Boston Number 2. Pp. 653; 59 illustrations. Philadelphia and London: W. B. Saunders Company, September, 1920.

THE first contribution of the *Medical Clinics* is that of Miss Ida M. Cannon, director of the social service department of the Massachusetts General Hospital and one of the leaders in this country in social service work. Her article is interesting and instructive, but it does seem that too great stress is placed upon the social factors in the management of these cases. For example, there is no doubt that social treatment is of great value in pernicious anemia. No one will gainsay that fact, but it is not the entire treatment of the condition, nor is it the most important treatment.

The next article, by Drs. White and Reid, is a very well-presented synopsis of the various physical findings in cases of mitral stenosis.

It would take too much space to mention in detail the seventeen other clinics which are incorporated in the present number of the *Medical Clinics*. It would not be amiss, however, to mention three of them which appear particularly helpful, dealing as they do with every-day medicine rather than with exceptional or unusual cases. Dr. White has a very comprehensive and thorough article on the modern examination of the stomach, while Dr. Ohler, in the

same careful manner, discusses the prognostic and diagnostic values of renal functional tests.

Lastly, Dr. Grover presents a really valuable discussion on the treatment of enuresis, one of the most difficult conditions with which the practitioner has to deal, unfortunately, as a rule, with poor results. J. H. M., Jr.

Die Tierischen Parasiten des Menschen. By Dr. Max Braun, Professor at the University of Königsberg, and Dr. Otto Seifert, Professor at the University of Würzburg. Part II, Klinik und Therapie. By Dr. Seifert. Second edition. Pp. 506; 19 illustrations. Leipzig: Curt Kabitzsch, 1920.

Braun's *Tierischen Parasiten des Menschen* has long been a classic in the field of parasitology. The fourth edition of that work, appearing in 1907, contained chapters on the clinical application of parasitology by Prof. Seifert. In the last edition the clinical chapters have been expanded into a separate work, corresponding to the fifth edition (1915) of Braun's *Parasiten des Menschen*.

The present volume, then, does not treat of the parasites themselves but rather of the diseases that they produce, and these are discussed from the standpoints of distribution, pathological anatomy, symptomatology, and therapy. The chapters follow the natural divisions of parasites, and include amebæ, flagellates trypanosomes, malaria, infusoria, the various classes of worms, arthropodes, and insects, but spirochetal diseases are omitted. The subject is handled in a somewhat unusual way, as the text consists of a summary of the work of individual observers all over the world; and authority is cited for almost every sentence, with full references in the footnotes at the bottom of each page. How skilfully this joiner's work must have been done will be evident when it is stated that the book is extremely readable and interesting. Indeed its peculiar value and unique position in the field of clinical parasitology depends on its full references to the literature. The author shows less than the usual German aversion to giving credit to foreign writers, though, since 1914, he has naturally not had very free access to foreign sources.

The usefulness of the book would have been greater if subheadings such as "Therapy," "Symptoms," etc., had been used, at least under the more important diseases. The quality of the paper is mediocre, but the type is very clear.

The book will be of first rate value to those doing special work on parasitic diseases, chiefly because of the excellent bibliography.

M. McC.

A Treatise on Materia Medica and Therapeutics, Including Pharmacy, Dispensing Pharmacology and Administration of Drugs. By the late Rakhaldas Ghosh. Eighth edition, by B. H. Deare, Lieut.-Colonel, Indian Medical Service, Officiating Principal and Professor of Medicine, Medical College of Bengal; Physician to the College Hospital; Dean of the Faculty of Medicine, University of Calcutta; and Birendra Nath Ghosh, F.R.F.P.S. (Glas), Examiner in Pharmacology, University of Calcutta; Fellow of the Royal Society of Medicine; Joint Author, *A Treatise of Hygiene and Public Health.* Calcutta: Hilton & Co., 1920.

Rakhaldas Ghosh was responsible for the first writing of this book. The title page of the present edition indicates that after his death its production has been entrusted to Lieut.-Colonel Deare and Birendra Nath Ghosh, both members of the Medical faculty of the University of Calcutta. This eighth edition is adapted to the new edition of the British Pharmacopeia.

The subject matter is treated in seven parts: Materia medica proper; pharmacy and dispensing; administration of drugs; pharmacology; materia medica and therapeutics; vaccine and serum therapeutics; and organotherapy.

In the present edition the drugs are arranged and classified according to their pharmacologic and therapeutic uses. This makes it an excellent book of reference for medical practitioners as well as students of materia medica and therapeutics. All of the information that one might wish to know about a drug is briefly given, including its source, characters, identification, incompatibles, composition, action, dose, pharmacology and therapeutics.

A complete index makes it a very admirable treatise, one, however, of more use to a Britisher than anyone else. T. G. S.

Electric Ionization: A Practical Introduction to its Use in Medicine and Surgery. By A. R. Friel, M.A., M.D. (Dub.), F.R.C.S.I.; Aural Specialist, Ministry of Pensions, London District; late Physician for the Throat, Nose and Ear, General Hospital Johannesburg; late Aural Surgeon and Bacteriologist, No. 1 South African General Hospital, B.E.F., France. New York: William Wood & Co., 1920.

"The first chapter of this book explains what is meant by ionization and describes how the electric current can be utilized to introduce drugs into the affected parts of the body for the treatment of disease; the second deals with the equipment necessary and a short space is devoted to making clear some electrical terms; the third

chapter details the effects of different "ions" and the fourth gives an account of technic suitable for applying ionization to different parts of the body."

Fifteen diseases of the skin: suppuration of the eye, ear and nasal sinuses, pyorrhea, inflammations of the urethra and vagina and other conditions are said to yield to this method of therapy. In spite of the fact that the author in his introduction denies that the ionization method is a panacea, this list seems a rather large one to be influenced by a single means of therapeusis.

The subject matter is complete and well presented. The claims made for this method seem unusually wonderful. T. G. S.

THE X-RAY ATLAS OF THE SYSTEMIC ARTERIES OF THE BODY. By H. C. ORRIN, O.B.E., F.R.C.S., Ed. Fellow of Royal Society of Medicine, London; Civil Surgeon attached Third London General Hospital, R.A.M.C.(T.). Pp. 91; 21 plates. New York: William Wood & Co., 1920.

THIS atlas consists of a series of plates made from negatives of a full-time fetus whose arterial system had been injected with a substance opaque to the *x*-rays. Accompanying each illustration is an explanatory text. The systemic arteries show in continuity, each one being designated by a pointer, and their origin, course, anastomoses and bony relationship are easily studied. At the end of the atlas is a series of stereoscopic plates which aid materially in the study of the larger plates. As an aid to the student of anatomy, this handsomely illustrated volume adequately fulfills its purpose. J. D. Z.

A SHORT HISTORY OF NURSING. FROM THE EARLIEST TIMES TO THE PRESENT DAY. By LAVINIA L. DOCK, R.N., in Collaboration with ISABEL MAITLAND STEWART, A.M., R.N.; Assistant Professor, Department of Nursing and Health, Teachers' College, Columbia University, New York. London and New York: G. P. Putnam's Sons, The Knickerbocker Press, 1920.

THIS interesting book is a condensation of the four volumes of the larger *History of Nursing*, written by Miss Dock in collaboration with Miss Nutting. It is planned especially for the use of student nurses. Certain of the more recent developments in the nursing world not to be found in the more elaborate work are to be found in this new book. Much has been enacted in recent years by the white-capped profession, and that much is partly dealt with in

Chapter XII under the heading of certain aspects of nursing in the world war.

The authoresses begin with the things known about the care of the sick in the ancient world and in turn discuss Christian, aristocratic and military influence in nursing. The story of Florence Nightingale and her times is told in what must appeal to the reader as the most interesting chapter of the book. Nursing in America and the inspiring story of Clara Barton furnish the material for another splendid chapter.

The reading of this book should furnish to nurses an inspiration in the consciousness of being one part of a great profession—a profession rich in romance and adventure which links the past and present with a future of greater possibilities. The nurse who knows not of the history of nursing works partly in the dark. T. G. S.

HANDBOOK OF DISEASES OF THE NOSE, THROAT AND EAR. FOR STUDENTS AND PRACTITIONERS. By W. S. SYME, M.D., F.R.F.P. and S.G., F.R.S.E., Surgeon to the Ear, Nose and Throat Hospital, Glasgow. Pp. 329; 26 illustrations. Edinburgh: E. & S. Livingstone. New York: William Wood & Co., 1920.

THIS little book is of the type popular twenty years ago in America but now largely superceded by works of greater pretentions giving more detail to the subjects discussed, although not attempting the discussion of so many. It is the old "Manual" for students and general practitioners and in no way differs from many of its predecessors, even containing the familiar list of "formulæ" at the end. Naturally enough in such a small volume the treatment of each subject must be most cursory and enough information is never given to enable anyone to care for a given and unfamiliar condition satisfactorily. For undergraduate students, perhaps, this work may be a guide and an index to classify for them the various diseases of the regions referred to and the outline of treatment given may answer the purpose. For post-graduate students or practitioners, it can have but little usefulness. G. M. C.

SOME CONCLUSIONS ON CANCER. By CHARLES CREIGHTON, M.D. Pp. 365; 114 illustrations. London: Williams & Norgate, 1920.

THE literature on the subject of cancer is ever increasing and were the amount of advance in our knowledge of malignancies commensurate with the increase in cancer literature, we should

be able to feel that we were approaching the goal toward which all eyes have been turned for many years, namely, the cause of cancer. The volume under consideration represents some conclusions of a man who has been more or less closely associated with cancer research for almost fifty years and who has a very broad knowledge of the literature, both past and present.

After a rather extensive introduction the author devotes the first section of his book to three types of malignancy which are used to illustrate principles. Thus, deciduoma malignum or chorionepithelioma represents a type in which a ferment action upon the blood reduces it to become a trophic substance so that blood-fed cells arise in the walls of the vessels and constitute one of the most malignant cancers known. In the second instance, mouse cancer is cited as a type of growth dependent upon a dyscrasic state of the blood due to excessive inbreeding. The third type described is the malignancy of the eyeball, supposedly due to the change of the cells which normally as a medium of nutrition into blood-feeding cells to a malignant end. The second part of the book is devoted to rather complete discussions of cancer as it occurs in various regions of the body. Frankly speaking, the book is not one that will appeal to the large majority of the profession as it is written by a laboratory man in laboratory language, hence it is unintelligible to the practical physician who has not been closely following cancer research. If it is the intention of the author to popularize his book, the reviewer would suggest a brief practical summary to each chapter so that the busy practitioner could get the conclusions quickly instead of being forced to read so many pages of obviously uninteresting theoretical considerations. F. B. B.

MANUAL OF PEDIATRICS. FOR STUDENTS AND DOCTORS. By DR. WALTER BIRK, Professor of Pediatrics, University of Tübingen. Vol. II, 4th ed. Pp. 338; 10 illustrations. Bonn: A. Marcus & E. Weber, 1920.

VOLUME I, recently reviewed, was devoted to the diseases of infancy. Volume II takes up the diseases of the remainder of child life. Very properly the author begins this volume with a complete consideration of the diet, care and nutritional disorders of older children. Diseases of the gastro-intestinal tract and the abdominal viscera are discussed in short but clear paragraphs. The acute infectious diseases, the so-called diseases of childhood as well as such infectious diseases as typhoid fever, tuberculosis, acute rheumatic fever and syphilis receive deserved attention. The diseases, requiring amplification of discussion, receive it, while

less severe or important ones are discussed briefly but lucidly. Diseases of the air passages, of the heart, of the nervous system, of the genito-urinary apparatus and diseases of the blood are presented to the reader in a most satisfactory manner. In his preface Dr. Birk apologizes for the absence of a section on diseases of the skin, but as he treats these so efficiently under the general headings, a chapter would seem superfluous. As a whole, the book is very valuable to a physician, but because of its general avoidance of detail, it is probably less valuable to the medical student. A. E. S.

PLASTIC SURGERY OF THE FACE. By H. D. GILLIES, C.B.E., F.R.C.S., Major, R.A.M.C., Surgical Specialist to the Queen's Hospital, Sidcup, etc. Pp. 408; 844 illustrations. London: Oxford University Press, 1920.

AT no one hospital of any of the allied forces was there such a rich mass of clinical material, nor were better facilities provided for the care of war injuries of the maxillofacial region, than at the Queen's Hospital, Sidcup. It was at this hospital that several of the more important advances in plastic methods were worked out and developed by Gillies and his colleagues. Among these may be mentioned the "tubed" pedicle flap, original with Gillies, the free epidermic inlay graft for replacing lost mucous membrane of the mouth, the epidermic "outlay" for reconstruction of eyelids, recognition of the necessity for an epithelial lining for rhinoplastic flaps. The superiority of the type of work being done at Sidcup was recognized by Surgeon-General Gorgas, who early in 1918, obtained permission to detail a number of American Army surgeons and dental surgeons as observers, and the knowledge gained there played an important part later in the facial restorations done on our own men.

The first thirty-four pages of the book are occupied with a consideration of the principles adopted by the author in plastic surgery of the face. The first principles governing the whole treatment of facial injuries are, diagnosis of the tissues involved, and replacement of all tissues as early as possible into their normal positions. Some valuable points are given in the formation of flaps to close defects. The question of anesthesia for these cases is taken up by Captain R. Wade, who prefers intratracheal ether or chloroform and oxygen through a nasal tube.

The greater portion of the book takes up in detail the repair of injuries of the various portions of the maxillofacial area, and consists largely of a description of individual cases. Almost every conceivable form of facial injury and its treatment is described and depicted in the illustrations. The diagrams of the operations

are particularly instructive. For restoration of missing portions of the mandible the writer prefers a graft from the crest of the ilium. Where the loss of bone includes the whole of the ascending ramus Gillies uses a piece of the seventh or eighth rib taken from the opposite side, including the costochondral junction and some of the cartilage. The maximum point of convexity forms a new angle of the mandible, while the ascending ramus is represented by that portion of costal cartilage which runs upward to the sternum. A false joint in the neighborhood of the glenoid fossa is made in this way, and a cosmetic and functional result thus accrues. A very important chapter deals with the prosthetic appliances, made by the dental surgeon, for maintaining the hard tissues in their correct alignment and for replacing those parts which cannot be restored by plastic surgery. The more important of these appliances include splints for fixation of fracture of the jaws and for supporting epithelial inlays, obturators for closing defects of the palate, nasal splints with dental fixation, as a support in rhinoplasty. In rhinoplasty, the Italian and French methods are discarded, in favor of either the Indian method or the horizontal forehead flap with superficial temporal pedicle. The final chapter points out the application of the experience gained in war injuries to the repair of facial deformity due to disease or injury incurred in civil life.

The book is the most complete that has been written upon this subject and one which no surgeon can afford to be without.

R. H. I.

DISEASES OF THE INTESTINE AND LOWER ALIMENTARY TRACT. By ANTHONY BASSLER, M.D., Professor of Gastro-enterology, Fordham University Medical College and New York Polyclinic Medical School and Hospital; Visiting Physician, New York Polyclinic Hospital; Visiting Gastro-enterologist, People Hospital. Pp. 660; 154 illustrations. Philadelphia: F. A. Davis Company, 1920.

DR. BASSLER has followed, most logically and successfully, his book on *Diseases of the Stomach and Upper Alimentary Tract* with the present work on *Diseases of the Intestines and the Lower Alimentary Tract*. However, the present addition to his published studies of the gastro-intestinal tract does not seem quite as thorough or carefully presented as his earlier book. Briefly, the first six chapters of the book deal with gastro-intestinal anatomy, physiology, chemistry, roentgenology, as well as the history and examination of the patient. The succeeding chapters deal with the various abnormal conditions within the intestinal tract as well as the pathological processes in the intestines themselves. Probably the most elaborate discussion is that which deals with the question

of intestinal toxemia. To this subject are assigned many pages filled with rather complicated suggestions as to diagnosis and treatment. It is certainly an open question as to the exact role which putrefaction within the intestinal tract plays in the production of symptoms, and while it may be conceded that it has such a role; nevertheless, it is impossible to concede rather didactic statements which attempt to demonstrate the existence of the various types of bacteria that are responsible for these symptoms, and to acknowledge that the symptoms can be cured by the production of vaccines prepared from these organisms. So little is definitely known about the life cycle, the type, the saprophytism, and so on of the bacteria of the small intestines, that treatment with vaccines does not seem to be the scientific method of treatment, to say the least. Furthermore, in the hands of Dr. Bassler, it might be possible, by bacterial methods, to isolate the offending organisms, but certainly, the technic, as the author gives it, is so difficult and so complicated that it would be utterly impossible for the average man to carry through, and this, in spite of the fact that the book is dedicated to the "practitioners of medicine, the best friends of the human race." While it is true that differences of opinion may exist between the author and reviewer, a natural result in discussing such a complicated subject as autointoxication, nevertheless the reviewer feels that in other respects the volume should prove of value to those who are interested in the subject of enterology as well as to those who are engaged in ordinary practice. It seems a pity that the subject of enteroptosis is not included in this book because it is such an important disorder, and those who do not possess the author's volume on *Diseases of the Stomach* will be without a discussion of this interesting protean subject. J. H. M., Jr.

A Practical Medical Dictionary. By Thomas Lathrop Stedman, A.M., M.D., Editor of the *Twentieth Century Practice of Medicine*, of the *Reference Handbook of the Medical Sciences*, and of the *Medical Record*. 6th revised edition. Pp. 1131. New York: William Wood & Company, 1920.

The sixth edition of Dr. Stedman's medical dictionary has been amplified by a large number of new words and new definitions, making the volume some twenty pages larger than the preceding edition. The reviewer had the pleasure of reviewing the fourth edition of this work, and all that he said at that time in commendation of the fourth edition holds for the present edition. A dictionary seems like a very dry and uninteresting compilation of words and definitions, yet truly no form of literary work requires more the scholary pen of one, who, like Dr. Stedman, is versed in all the sciences, from paleontology to philology, from psychology to syndesmology. J. H. M., Jr.

PROGRESS
OF
MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

W. S. THAYER, M.D.,

PROFESSOR OF CLINICAL MEDICINE, JOHNS HOPKINS UNIVERSITY, BALTIMORE, MARYLAND,

ROGER S. MORRIS, M.D.,

FREDERICK FORCHHEIMER PROFESSOR OF MEDICINE IN THE UNIVERSITY OF CINCINNATI, CINCINNATI, OHIO,

AND

THOMAS ORDWAY, M.D.,

DEAN OF UNION UNIVERSITY (MEDICAL DEPARTMENT), ALBANY, N. Y.

The Heart and its Rhythm in Acute Rheumatism.—PARKINSON, GOSSE and GUNSON (*Quart. Jour. Med.*, 1920, xiii, No. 52, 363–379) recall the frequency of endocardial and myocardial disease initiated during an attack of acute rheumatism and the difficulties encountered in diagnosing the latter condition. Their investigation consisted in a search for signs indicating acute myocarditis and eventual myocardial disease likely to determine heart failure, in 50 cases of acute rheumatic fever. All other available physical signs were noted. The size of the heart, as indicated by the apex beat, varied but little and from their studies the authors conclude that the frequency and degree of enlargement of the heart during an attack of rheumatic fever have been exaggerated. No relationship was found between the development of systolic murmurs at the apex and demonstrable cardiac enlargement. Sinus arrhythmia was present after the attack in 47 cases (94 per cent.). It occurred in 2 cases with a pericardial rub, 1 case with a pericardial effusion, 1 after flutter and in each of 15 cases which had developed acute heart-block. They (authors) feel therefore that the presence of sinus arrhythmia does not indicate that the heart has escaped infection. Premature auricular contractions occurred in 7 cases (14 per cent.). Paroxysmal auricular flutter occurred in 1 of these. Auricular fibrillation did not occur during the disease in any of the cases. The authors conclude that auricular disease (such as fibrillation and flutter) is often the sequel of acute rheumatism; that the frequency of extrasystoles in this infection and their association with flutter and heart-block suggest that they indicate acute myocarditis. Some degree of auriculoventricular heart-block developed in 15 cases (30 per cent.). Of these 11 (22 per cent.) showed delayed conduction only, the

remaining 4 showed partial heart-block with dropped beats, and in 1 of them the degree of 2–1 heart-block. These phenomena invariably disappeared during convalescence. The observers conclude that heart-block is common in rheumatic fever; that it indicates acute myocarditis; that it may, therefore, be premonitory of chronic myocarditis and eventual heart failure.

Cerebrospinal Fever.—The importance of the anti-endotoxin content of antimeningococcus serum. GORDON (*Med. Research Council*, London, 1920, 93–109, Special Report Series, No. 50), in the course of his studies, found that an important factor in the pathogenicity of the meningococcus consists of a powerful toxic agent closely bound up with the bacterial protein. This endotoxin is liberated either by an external lysin or by the autolytic enzyme contained within the coccus itself. That the efficiency of an antimeningococcus serum is modified greatly by the quantity of anti-exdotoxin it contains is illustrated by the results obtained in the treatment of a series of cases in the London district. Here the mortality was 18.5 per cent. as contrasted with a mortality of 48 per cent. elsewhere. Investigation of the serum used in this district revealed the fact that its anti-endotoxin titer was high, whereas the sera used elsewhere possessed little or none as revealed by protection experiments. Later it became necessary in this same district to introduce a different lot of sera. The mortality immediately rose to approximately 50 per cent. From his studies Gordon concludes that anti-endotoxin is the most important individual antibody identified so far in antimeningococcus serum. He feels that the conception that cerebrospinal fever is a disease in which one of the essential features is the struggle between the endotoxin of the infecting agent and the ability of the patient to form anti-endotoxin brings this disease into line with infections in which serotherapy has achieved some of its greatest successes. At the time of this report the anti-endotoxin content of type i (Gordon) antimeningococcus serum was much higher than that of the type ii (Gordon) antiserum and the therapeutic results correspondingly better. Further work on anti-endotoxin serum for type ii infections is being carried out.

Diffuse Adenomatosis of the Thyroid Gland.—GOETSCH (*Endocrinology*, Los Angeles, 1920, No. 3, iv, serial No. 15, 389–402) reports the study of "borderline cases" in which the familiar syndrome of hyperthyroidism is present (asthenia, loss of weight, nervousness, labile pulse, mild tachycardia, perspiration and tremor, occasionally depressions, often hyperpyrexia) but in which physical examination reveals no gross thyroid gland changes and no eye signs. The diagnosis in these cases lies between mild hyperthyroidism, incipient tuberculosis, various forms of psychoneuroses and perhaps certain chronic infections. In a series of 15 such cases in which the usual medical treatment had failed and which gave a positive epinephrin hypersensitiveness test the author advised operation—usually consisting of a bilateral partial resection of the thyroid gland. The author reviews briefly the accepted pathological change occurring in the gland which are associated with hyperthyroid symptoms: (1) Slight or moderate hypertrophy and hyperplasia of the alveolar epithelium surrounding the colloid, giving

rise to a mild hyperthyroidism such as occurs in association with the hyperplastic gland of puberty, pregnancy, menstruation, etc.; (2) more advanced alveolar parenchymal hypertrophy and hyperplasia, as in exophthalmic goiter; (3) discrete thyroid adenomata arising probably from individual groups of the interstitial epithelial cells (Wölfler) which occur in the interstices between the normal acini. To this classification of pathological thyroid changes associated with hyperthyroidism Goetsch adds a fourth which he calls "Diffuse Adenomatosis," and which is characterized by a general overgrowth of the interstitial cells (Wölfler) and hyperplasia of the acinar epithelium, as contrasted with the circumscribed overgrowth of the former which results in discreet adenomata. He reports 15 cases, mostly young adults, presenting a syndrome characteristic of possibly hyperthyroidism, incipient tuberculosis, neuro-circulatory asthenia and allied conditions. Eye signs and positive clinical findings in the thyroid gland were absent. They failed to respond to medical and hygienic treatment. Many failed to show increased basal metabolism. All gave positive reactions to the epinephrin test. Ten of of the fifteen cases had had sanatorium treatment for tuberculosis; one was a case of paroxysmal tachycardia; one a case of weakness, nervousness and tremor of unknown origin; three complained primarily of nervousness and weakness. In each case an extensive bilateral partial lobectomy was performed, about three-fourths of the gland substance being removed. The glands from these cases showed fairly uniformly the changes which lead the author to introduce the term "Diffuse Thyroid Adenomatosis." The patients so treated showed from a moderate to a very remarkable improvement.

Metabolism in Tuberculosis.—McCann and Barr (*Arch. Int. Med*,. 1920, xxvi, 662) give a detailed report of clinical calorimetric determinations on 15 cases of pulmonary tuberculosis, which they summarize as follows: "(1) The basal metabolism of tuberculous patients may be normal or very slightly above that of normal men of the same size. Thus, in 10 cases, the variation from average normal was from minus 3 to plus 15 per cent. (2) Further increases in metabolism occur with a rise of body temperature. These increases are not large. Thus 1 case was given in which the temperature rose 1° C. during two hours without a chill. The heat production of the second hour was only two calories greater than that of the first hour. With a rectal temperature of 104° F., the metabolism may be 30 per cent. above the average normal. (3) The basal heat production in tuberculosis may be less than the normal for the same patient when in health; in other words, the loss in weight may be accompanied by a reduction in metabolism which more than compensates for the tendency to increase caused by the disease. (4) Limited data regarding the nitrogen excretion show that, while a toxic destruction of protein does exist in tuberculosis, it is not large. The urinary nitrogen may be reduced to from 5 to 6 gm. per diem, though nitrogen balance may be attained only at a higher level (about 10 gm. a day). (5) The specific dynamic rise in metabolism produced in 2 cases by the ingestion of a protein meal corresponded closely with that produced by the same meal in three normal men." *Conclusions.* In view of the fact that the food requirements of tuberculous patients are not large, either as regards total energy value or

nitrogen content, forced feeding is unnecessary and is probably harmful in the active stages of pulmonary disease. Since protein increases the respiratory exchange in the tuberculous as in normals it may be well to limit the protein intake during periods of activity (of the disease) in order to put the lungs at rest.

SURGERY

UNDER THE CHARGE OF

T. TURNER THOMAS, M.D.,

ASSOCIATE PROFESSOR OF APPLIED ANATOMY AND ASSOCIATE IN SURGERY IN THE UNIVERSITY OF PENNSYLVANIA; SURGEON TO THE PHILADELPHIA GENERAL AND NORTHEASTERN HOSPITALS AND ASSISTANT SURGEON TO THE UNIVERSITY HOSPITAL.

The Treatment of Chronic Empyema.—TUFFIER (*Annals of Surgery*, 1920, lxxii, 3, 266) gives us his conclusions, based on 91 cases of empyema which he operated on from August, 1914 to December, 1919. Exploratory puncture to determine the bacteriological nature of the effusion is of first importance. Pneumococcic pleurisies are mild and often cured by simple aspiration, while streptococcic pleurisies are grave and most often require thoracotomy. If repeated punctures leave a residuum as shown by radioscopy, thoracotomy is done in the postaxillary line. Evacuations of the effusions and disinfection of the pleura follow. Some cases can be closed immediately. Large cavities are dakinized. All of Tuffier's cases have been seen from six months to three years after operation. Thoracic deformity was slight. Chronic pleurisies are exceptional when acute effusions are well treated. Costal resection in the treatment of chronic empyema should be reduced to a minimum. Closure of the surgical incision and pleural decortication should be preceded by disinfection of the cavity.

Roentgenographic Appearance, Diagnosis and Pathology of Some Obscure Cases of Bone Lesions.—LOVETT and WOLBACH (*Surgery, Gynecology and Obstetrics*, 1920, xxxi, 2, 111) very carefully report with pathological findings 25 cases with obscure bone lesions. The cases presented are those in which there was, in the minds of the writers, doubt as to the correct diagnosis from the *x*-ray and other data available before operation. Considering the behavior of bone in general, as studied by the *x*-ray, it seems to be a structure of very limited reaction to pathological conditions. There seem to be only three reactions possible in bone: (1) atrophy or diminution in lime content; (2) destruction of bone tissue, local or general; (3) a formative process, characterized by the formation of new bone, or a condensation of existing bone around a focus of disease. The errors in diagnosis in the experience of the writers has been in mistaking tuberculosis for other things. The other troublesome confusion was between osteomyelitis and syphilis. The serious problem of differential diagnosis occurs most often in cases

in which focal lesions are present, in which the phenomena of formative and destructive activity have become so mixed that without pathological examination, in many of them diagnosis is impossible. The advantage of such a diagnosis made during operation is evident to the surgeon because it guides him in the treatment of the bone cavity. The diagnosis of infectious lesions of the bones would be simple if each infectious agent produced the same reaction. The pyogenic bacteria alone may be counted on to conform to this type. Syphilis affects the bone in two ways and results either in destruction of the bone or the new formation of bone. In tuberculosis of bone there may occur: (1) exudate, fibrinous or puriform, (2) discrete proliferative lesions, (3) a diffuse proliferative reaction, essentially tuberculous granulation tissue. Tuberculosis may simulate any other infectious process in location and character of the lesion. Diagnosis from *x*-ray studies alone is occasionally impossible.

The Treatment of Chronic Empyema.—HEDBLOOM (*Annals of Surgery*, 1920, lxxii, 3, 288) says chronic empyema has been recognized and treated during twenty-six centuries, but it is only sixty years since the first rib resection for drainage was done. The successive stages in the progress of treatment since that time are as follows: Increasingly radical treatment, designed to obliterate the cavity by the collapse of the chest wall, involving successively more extensive operations, and culminating finally in a complete radical resection. A conservative trend manifested primarily in the modifications of the complete resection, but more in the attempt to preserve the chest wall and to restore the lung to its structural and functional relationships as first advocated by Delorme. The adaptation of the Carrel-Dakin hypochlorite solution technic to the treatment of chronic empyema cavities. Chronic empyema is a disease which is not incompatible with life nor with a fair degree of health and usefulness. The principles of treatment should, therefore, be first, the preservation of life, and second, as far as possible, the conservation of function. Shortening convalescence, while very desirable, should always be a subsidiary consideration. The choice of treatment must be made with cognizance of the variable etiology and pathology of the process, and the general condition of the patient. A major procedure is indicated only if non-operative or less extensive surgical treatment reasonably may be considered less effective. In case of sinuses and small cavities, adequate drainage is usually sufficient to effect a cure with or without short preliminary hypochlorite solution treatment. It is at least open to question whether a radical operation is indicated in these cases for the sole purpose of shortening convalescence at the risk of an appreciably increased mortality. Dakin's hypochlorite solution treatment is the method of choice in the treatment of the ordinary type of chronic empyema cavity of any size, for the following reasons: The general condition of the patient is, as a rule, improved to a remarkable degree. The cavity may be obliterated or greatly reduced in capacity by the liberation and expansion of the lung (resulting from the treatment). If the lung expands in part the extent of a later operation will be proportionately reduced. If the lung entirely fails to expand, the cavity will have become relatively sterile in preparation for operation, thereby lowering postoperative morbidity and

mortality. Pulmonary decortication will be materially facilitated in some cases, owing to the softening action of the solution on the visceral pleura. A pulmonary decortication through a rib-spreading exposure after preliminary hypochlorite solution irrigation is the most conservative treatment for cavities that are not obliterated by drainage or Dakin's solution treatment alone. If such an operation is successful, the lung is restored to its normal structural and functional relationship, thereby obliterating the cavity. If the operation is only partly successful, the magnitude of a secondary destructive operation is proportionately decreased. Since it is impossible to judge with certainty before operation of the relative expansibility of the lung in every recent nontuberculous case, a decortication should be done rather than a destructive operation, thereby giving the patient the benefit of the doubt. If the lung does not expand, or if a considerable cavity persists following decortication, a plastic operation is indicated. If the cavity is of considerable extent or the patient debilitated, a two- or three-stage plastic operation is to be recommended. The recognition of tuberculous empyema is often difficult. A history of a primary pleurisy with effusion seems more often to signify a tuberculous condition than does a pulmonary lesion, unless the latter is active and extensive. A tuberculous empyema may be present in the absence of clinical or *x*-ray evidence of pulmonary involvement. The typical microscopic picture in the sectioned pleura or the demonstration of the bacilli in the exudate may constitute the only evidence in such cases. A tuberculous empyema not secondarily infected should not be drained, and should be aspirated only for a considerable accumulation of fluid. For a tuberculous empyema secondarily infected, either by operation or spontaneously, drainage is necessary. In the absence of bronchial fistulas and of bleeding, secondarily infected tuberculous empyema may be markedly benefited by antiseptic solution treatment. The amount of fibrosis or other pathologic change in the lung in such cases determines the degree of expansion of the lung, whether following antiseptic solution treatment or decortication. If the lung fails to expand in whole or in large part, a several-stage operation designed to collapse the chest wall is indicated. Tuberculous patients are relatively poor operative risks. Adequate drainage is the first indication in cases of empyema cavities which are draining through large bronchial fistulas. The fistulas may be obliterated spontaneously following such treatment. Operative closure of bronchial fistulas that persist is necessary to complete healing. It may be accomplished by decortication of the involved portion of the lung with cautery, suture, or skin plastic to cover the opening of the fistula. Occasionally healing results from simple granulation of surrounding tissue after destruction of the epithelial lining of the bronchial stoma. Closing the bronchus that is draining pus from within the lung may result in a secondary lung abscess. A large bronchial fistula is a contra-indication to Dakin's solution treatment. Sinuses of variable duration are common following more or less complete obliteration of empyema cavities; a large proportion eventually are obliterated without radical treatment; for those which persist, plastic operation is indicated. Operative mortality in chronic empyema has been due largely to shock and infection. Reduction of the extent of operation and preliminary sterilization will materially lower this mortality.

PEDIATRICS

UNDER THE CHARGE OF

THOMPSON S. WESTCOTT, M.D., AND ALVIN E. SIEGEL, M.D.,

OF PHILADELPHIA.

An Unusual Case of Cretinism.—KERLEY (*Arch. Ped.*, August, 1919) reports a case of a girl, aged eight and a half years, who weighed forty and a half pounds. She was thirty-seven and a half inches tall. She was a full term baby and weighed four and a half pounds at birth. She was breast fed for seven months and then bottle fed. Her growth was slow and she appeared backward in her development. Dentition began fifteen months, and she did not walk until her third year. Her appetite was always poor and there was habitual constipation. She was dull and inactive and took but little interest in her surroundings. On physical examination the heart, lungs, kidneys and blood were found to be negative. The abdomen was large and protuberant, and there was an umbilical hernia. The hair was dry and coarse and the nose flat and the lips thick, the skin dry and harsh and cool to the touch, the teeth poorly formed and decayed. The second set had not appeared. She could say only a very few words, had no interest in play nor in other children. She showed all of the classical signs of cretinism and was given a suitable diet and placed on one grain of thyroid extract twice a day. This was later reduced to a half grain. In a year and thirteen days she gained eight and three-quarter pounds in weight and grew six and five-eighth inches. Her mental improvement was remarkable and kept pace with the change for the better in physical appearance. The change in the character of the hair was most noticeable and the large umbilical hernia disappeared.

Some Remarks on Cranial Sinus Thrombosis in Children.—OPPENHEIMER (*Arch. Ped.*, January, 1920) reminds us there are two recognized forms of thrombosis—primary or marasmic; and secondary or infective or inflammatory. The latter is the more frequent type. The primary type usually is located in the longitudinal sinus, rarely in the lateral and still less frequently in the cavernous. It occurs during the first two years of life and more especially during the first six months. The diagnosis of primary sinus thrombosis in children is difficult and is seldom made during life. Secondary or infective sinus thrombosis is much more frequent than the primary form, and follows extension of inflammation of parts contiguous to the sinus wall. It occurs almost as frequently in children as in adults. It generally affects one of the dual sinuses. In its later stages it is often associated with meningitis, and not rarely with small cerebral or cerebellar abscesses. The most frequent causes are the suppurative middle ear lesions. Males are affected more frequently than females, and the right lateral sinus is more frequently involved than the left. This is probably because the right is usually larger and closer to the mastoid cavity than the left. The symptoms are fairly constant, although in children they may be

masked by the presence of some underlying acute infectious condition. The temperature may be high. Chills are absent as a rule. The hands and feet may be often found to be cold. An important point is the taking of a two-hour temperature in order to note accurately the varying oscillations. Typical cases occasionally present themselves where the temperature remains steadily high without much remission. In older children there may be headache, pains in the occipital region, and tenderness on palpation along the jugular vein. A diagnostic sign of importance is the unilateral enlargement of the lymph nodes at the junction of the facial vein with the internal jugular. The cord-like feel along the border of the sternocleidomastoid is quite typical. There is often nasal hemorrhage. Drowsiness is frequent. Dysphagia is an important symptom. The treatment is entirely surgical.

Fluid Injections in Dehydrated Infants.—McLean and Lang (*Am. Jour. Dis. Children*, May, 1920) treated 76 infants showing signs of dehydration by giving fluid injections. These 76 children received 269 injections of fluid. Of these 155 were hypodermoclyses, 92 were intraperitoneal injections and 22 were sinus injections. The mortality was 56.5 per cent. The amount of clyses varied between 90 and 150 c.c., depending on the size and the condition of the child. In a few cases $\frac{1}{1000}$ to $\frac{1}{500}$ grain of atropin was used in the solution. On one occasion 120 c.c. of a 6 per cent. dextrose solution was used. The intraperitoneal injection fluids were of various formulæ, varying in amount from 150 to 240 c.c. Their records show worse results in infants receiving more than three injections than in those receiving less than three injections. In spite of this it was found that repeated injections usually do no harm. There was no relation between the weight of the infant and the mortality rate. The mortality was considerably higher in infants who showed a weight loss twenty-four hours after injection than in those who maintained their weight or gained. There was no marked difference in the death-rate of different age groups. A change of ten in the pulse-rate, of five in the respiration and of 1° of temperature are definite signs of reaction. The pulse was more frequently affected after sinus and intraperitoneal injections than after hypodermoclyses. The respiratory rate was more frequently affected in peritoneal injections than after sinus injections or hypodermoclyses. The temperature was more frequently affected after sinus injections. Weight gains were more frequently noted after intraperitoneal injections. It was also noted that the shorter the interval between the onset of symptoms and the beginning of treatment, the greater was the response.

The Value of Luetin in an Out-patient Department.—Meyers (*Arch. Ped.*, April, 1920) tested 168 cases, of which 61 per cent. were males and 39 per cent. were females. The ages varied from eighteen years to seven weeks. The total number of positive reactions was 65.4 per cent. In practically every case that gave a positive reaction with the luetin test there was something in the history or physical findings indicative of syphilis. The family history suggested lues in 35 per cent. of the cases, while 30 per cent. was diagnosed from the clinical findings. The various reactions to luetin may be grouped under five distinct heads: papular, vesiculopustular, delayed or torpid, urticarial and hemorrhagic. The majority

were papular. After forty-eight hours there appeared at the site of injection a definitely indurated papule, 5 to 12 mm. in diameter, usually surrounded by a zone of redness of varying size. Over one-third were of the pustular type. In this type an indurated papule appeared in two or three days. It soon became vesicular, and after central softening this became a pustule, which ruptured and formed a scab. Several cases gave the delayed or torpid reaction. The primary papule soon disappeared and simulated a negative reaction. In ten to twelve days it reappeared and progressed to either a definitely indurated papule or a pustule, after which it followed the progress of the particular type. There were 3 cases of urticarial type. In about nine days after injection the lesion took on a distinct urticarial form about 8 mm. in diameter. In a few days it changed to a papule. There were only 2 cases of the hemorragic type. Instead of the lesion filling with pus it contained a hemorrhagic exudate. The test is a simple matter if the injection is made intracutaneously, and 65 per cent. of congenital luetics will react positively to the test. There are no constitutional reactions.

The Diagnosis and Treatment of Congenital Pyloric Stenosis.—HARDT (*Penna. State Med. Jour.*, May, 1920) says that this condition undoubtedly exists much more frequently than is diagnosed. The first symptom is vomiting, which frequently begins as regurgitation and gradually becomes worse until it become distinctly projectile in character. It occurs after each feeding or after several retained feedings. The character of the vomitus is not distinctive. The vomiting is the most alarming symptom. There is a peristaltic wave which appears after food is taken and radiates from the cardia to the pylorus. A tumor may be felt to the right and above the level of the umbilicus. There are scanty stools and urine and progressive loss of weight. Fluoroscopic examination is of great value in making the diagnosis, and it is further of value in determining whether or not the case is one for surgical treatment. The fluoroscopic technic consists of giving a small amount of bismuth in mothers' milk with the child in the horizontal position. While nursing from the bottle the mixture is watched as it passes through the esophagus into the stomach. The baby is rotated toward the right side, and as the bismuth gravitates toward the pyloric end of the stomach, peristaltic waves commence to be visible in the pyloric antrum and the pylorus. A small amount of bismuth is forced through, and as the pylorus closes tightly, peristaltic contractions can be seen which are independent of the rest of the stomach. The examination is repeated at the end of two hours and again at the end of four hours. If at the end of this time one-half of the bismuth remains in the stomach the case is considered a surgical one. The chief condition simulating this and which must be differentiated in diagnosis is pylorospasm. The most significant point in pylorospasm is that the vomiting and the peristalsis are much less marked, and it is usually observed in much older children. There is always absence of tumor in pylorospasm.

Intussusception in Infants.—EPSTEIN (*Ohio Med. Jour.*, June, 1920) reports 5 cases; 4 of these occurred in the summer, which fact together with the acute onset suggested gastro-intestinal inflammatory disease rather than intussusception. The alarming symptom for which medical

advice was sought was the hemorrhage from the rectum. The differential diagnosis from a follicular enteritis, the only form of gastro-enteritis in which blood is present in the stools, is made by the presence of shock, a normal or subnormal temperature, absence of stools, a palpable tumor and a mass on rectal examination in intussusception. Rectal examination should be made in every case, with a history of blood in the stools. Another very important examination, that of the napkin, to ascertain whether there is a stool present with the hemorrhage or whether there is hemorrhage without a stool. The latter is indicative of intussusception.

The Influence of Epidemic Poliomyelitis upon the Susceptibility to and the Symptomatology of Other Contagious Diseases.—REGAN (*Arch. Ped.*, May, 1920) says that the occurrence of mixed infection constitutes a possible source of danger in the hospital treatment of all contagious diseases. This was considered particularly important as large numbers of children were admitted to the hospitals during the epidemic of 1916, at the ages of the greatest susceptibility to contagious diseases. Many gave no history of a previous illness. This was during a period of the year when contagious diseases were prevalent. Rashes of scarlatiniform type, with heavily coated tongue, congested throat and occasional minute spots on the buccal mucosa, which occur as part of the symptomatology of poliomyelitis, caused some confusion at first and many were isolated as possible cases of measles or of scarlet fever. The subsequent course of the cases showed that these phenomena were to be attributed to poliomyelitis. As the epidemic progressed the small incidence of mixed infection was noted. Regan observed in the Kingston Avenue Hospital only 15 cases developing a mixed infection, or 0.83 per cent., and if 9 cases of pertussis were excluded, only 0.33 per cent. These 15 cases were 9 of pertussis, 3 of diptheria, 1 of measles, 1 of scarlet fever and 1 of varicella. No other children in the wards developed infections from contact with these in spite of the fact that the wards were filled with children, the majority of whom were unprotected by previous attacks. Not only was mixed infections of poliomyelitis with other contagious diseases slight, but the number of patients admitted with double infections of this and other contagious malady was also small. There were only 17 cases, or 0.94 per cent. Thus out of 1798 patients only 32 had on admission or developed subsequently another disease. The incidence percentage was 1.72. There were 22 with pertussis, and if these were deducted the incidence percentage would be only 0.59 per cent. These facts indicate that children with poliomyelitis are not as susceptible to develop other contagious diseases as are normal children, with the possible exception of pertussis Regan offers the following working theory: Upon infection with the virus of poliomyelitis, certain changes occur in the tissues of the infected individuals, due possibly to the products of growth of the organism of poliomyelitis, which render them unsuitable for the development of the causative agents of other acute infectious diseases. In other words a condition of antagonism exists. It may be that the causative factor of poliomyelitis is so thoroughly distributed and so numerous in the nose, throat and upper respiratory tract that the infectious agents of the other acute infectious diseases find it difficult to find an atrium

in which they can develop sufficiently to invade the body. The only germ that seems to have a symbiotic relation with that of poliomyelitis is the bacillus of whooping-cough. The influence of poliomyelitis on the symptomatology of scarlet fever, diphtheria, varicella, measles and parotitis seems to be negligible, with the one exception that the symptoms of the associated disease seem more mild than is usual. The mortality rate of the mixed infections was very low, being only 3 per cent. as compared to 23.79 per cent. in the uncomplicated cases.

Biological Study of the Hemolytic Streptococcus from the Throats of Patients Suffering with Scarlet Fever.—BLISS (*Bull. Johns Hopkins Hosp.*, May, 1920) reports that in a study of 25 strains of Streptococcus hemolyticus, isolated from the throats of patients with scarlet fever, 20 strains, or 80 per cent., were agglutinated by four different antistreptococcic sera made with streptococci obtained from scarlet fever cases. None of these strains were agglutinated by five antistreptococcic sera of non-scarlatinal origin. Only three of seventeen strains of non-scarlatinal origin were agglutinated by these three sera of scarlatinal origin, and they may have been either atypical scarlatinas or scarlatinal contacts. There were certain differences in structural characteristics, particularly in the fermentation of carbohydrates. From this study it would appear that a great majority of strains of Streptococcus hemolyticus isolated from the throats of scarlet fever patients belong to a specific biologic type as determined by the reaction of agglutination. It is possible that the heterogenous strains found may be accidental dwellers in the throat and that a more careful selection of the colonies may reveal a still higher proportion of unit type organism.

The Effect of Intravenous Injections of Calcium in Tetany, and the Influence of Cod-liver Oil and Phosphorus in the Retention of Calcium in the Blood.—BROWN, MCLACHLAN and SIMPSON (*Am. Jour. Dis. Children*, June, 1920) report observations on 14 cases of frank tetany, all of which showed varying degrees of rickets. They studied the blood calcium of 18 infants under one year of age. Then they observed the effect of intravenous injections of calcium acetate on blood calcium and on the symptoms of the cases of tetany and also the effect of cod-liver oil and phosphorus in the blood calcium and the clinical result. Constitutional reactions were produced following intravenous injections of calcium lactate in 1.25 gm. doses. The degree of reaction varied from the slight drowsiness to almost complete collapse, accompanied by dyspnea. The signs of reaction disappeared usually between one and seven hours; the more severe the reaction the more longer it took the patient to recover. Intravenous injections of calcium lactate in 1.25 gm. doses produces a temporary absence of both electric and mechanic signs of tetany, usually lasting from seven to ten hours. Calcium lactate injected intravenously apparently exerts no beneficial therapeutic effect, unless supplemented by the administration of cod-liver oil and phosphorus, and by this method the reduction of the tetanoid symptoms is a little more rapid than by the use of cod-liver oil and phosphorus alone. Cod-liver oil and phosphorus produces an increase in the blood calcium with a corresponding reduction in the mechanic and electric signs within a period of from ten to seventeen days.

OBSTETRICS

UNDER THE CHARGE OF

EDWARD P. DAVIS, A.M., M.D.,

PROFESSOR OF OBSTETRICS IN THE JEFFERSON MEDICAL COLLEGE, PHILADELPHIA.

The Diagnosis of Early Ectopic Pregnancy.—HEANEY (*Am. Jour. Obst.*, July, 1919) contributes a paper in which he analyzes the signs and symptoms of early ectopic pregnancy. He draws attention to the widespread opinion concerning appendicitis, and states that the medical profession is not equally alert regarding ectopic pregnancy. The family doctor is, as a rule, unfamiliar with the symptoms, so that when cases come to the specialist they have frequently been neglected. This is a condition which certainly deserves remedying. The education of the public is necessary, and students should be given a different conception of diagnosis and symptoms in these cases from that which is usually given in text-books. More attention should be given to the early unruptured cases. Stress has been laid for some time on cases that have ruptured and in which hemorrhage is present, and the student gets the idea that such cases constitute a majority of those that he will see. Very often ectopic pregnancy is not thought of unless the condition of the woman is serious. Most articles in books describe the pain as stabbing, tearing or lancinating. When a tube actually ruptures extreme pain is the rule. Before this, however, patients usually have more or less discomfort, backache or cramps, or an indefinite time before rupture oftentimes attacks of pain which are thought to be gas in the intestine have occurred at an indefinite period before operation. These cramps are intermittent and appear and reappear usually a few days before the case terminates in rupture. If in the subject of ectopic pregnancy the emphasis is to be laid on the severity of the pains it is like dwelling on the emaciation of a patient in cancer of the uterus. Evidently in such cases delay may be fatal. In the experience of the writer one patient who had ectopic pregnancy had not the slightest pain or discomfort. The patient's only complaint has been of intermittent bleeding of a month's duration. When the patient has gone to her regular period and then complained of cramps in the side of the pelvis or of gas pains it should be looked upon as possibly an ectopic pregnancy. Again, too much stress in taking histories is laid upon the existence of amenorrhea. The first suspicion of pregnancy is in the passing of the menstrual period and most of the cases coming to clinics with ectopic pregnancy, if a careful history is taken and the patient is questioned closely the fact that she has been irregular in menstruation will be elicited. The ordinary history is deficient in this as it usually states only that the patient is menstruating or has just menstruated. The obstetrician familiar with the inaccuracy of statements made by patients can usually by taking a good history and questioning the woman discover the real condition. Furthermore, on close questioning it will be found that the belated menstrual period was less in quantity and shorter in duration than normal. It is exceptional in ectopic

pregnancy to have profuse bleeding for a long time, but intermittent bleeding over a considerable period should arouse suspicion. The discharge may be only a bloody liquid discharge, with or without clots. As irregular bleeding is unusual the patient is liable to forget that she went over her regular period. If the patient was pregnant she usually ascribes the bloody discharge to the fact that in her own mind she fears that she is about to have an abortion. Every patient who has suspicious symptoms of threatened, imminent or incomplete abortion should be examined, with the possibility in mind that an ectopic pregnancy may be present. A diagnostic point of some importance is the fact that the patient will often refer cramps to the side of the pelvis rather than over the uterus. Students should be taught that this irregular bleeding is more typical of ectopic pregnancy than is the amenorrhea. Undue emphasis has also been placed upon the passage of a cast of the uterus or similar portions of decidua. It is difficult to obtain from the patient accurate statements as to what has actually been discharged from the uterus. While shreds of decidua may have been expelled they are usually passed with blood clots, so that the patient knows nothing about the fact that they have been discharged. It is also commonly taught that scrapings by the curette and pieces of membrane when examined microscopically give ground for making an exact diagnosis. It is often stated that if a uterine pregnancy is present, villi of the chorion will be found; but if the pregnancy is extra-uterine, decidual cells without villi are seen under the microscope. The absence, however, of chorionic villi in the discharges does not prove that a uterine pregnancy has not happened. There is no certainty in the examination of any pieces of expelled tissue. While the presence of chorionic villi proves that uterine pregnancy exists the absence of this villi does not prove, unless the complete decidual lining has been examined and a careful search reveals that no villi can be found. There is no certainty in examining pieces of expelled tissue only. After it has embedded itself in the decidua several weeks are required to bring the chorion in apposition to the decidua in all parts of the uterus. Before this occurs pieces of decidua may be expelled in uterine pregnancy, and should this decidua be festooned over the site of implantation then microscopic examination will not show villi of the chorion. While the presence of villi of the chorion is proved by intra-uterine pregnancy the absence of this phenomenon does not rule out uterine pregnancy. If a suspicious case be curetted and no decidua found this does not necessarily completely rule out pregnancy, for the uterus may have expelled its contents and the curette failed to obtain material for examination. This is especially true if the embryo is dead. In some cases of membranous dysmenorrhea without pregnancy decidual cells are found. Very few ectopic pregnancies pass any membranes as such, and in general it may be said that if the patient can give a clear history of having passed organized tissue the more likely it is that the case is one of uterine rather than ectopic pregnancy. One fallacy in current teaching is that the uterus enlarges in ectopic pregnancy. If this were to be true the ectopic pregnancy under these conditions, should the pregnancy go to near term, the uterus would be about as large as an ordinary pregnancy at the fourth month. The closer the ectopic sac is to the uterus the more rapidly does the uterus enlarge. As ectopic pregnancies are very

commonly interrupted early it is seen that enlargement of the uterus may in many cases be absent. At operation there is usually some enlargement of the uterus in a considerable percentage of cases, but in a large number the uterus is not above average size and frequently is less than the average. This may arise from the fact that ectopic pregnancy is most liable to develop in cases in which the development of the generative tract has been deficient. If the uterus be not enlarged and smaller than usual, if the patient has colicky pains and intermittent bleeding, the diagnosis of ectopic pregnancy may be on the average safely made. Again, the fact that the patient denies nausea or symptoms associated with the breast is not evidence of ectopic pregnancy. Should, however, nausea and breast symptoms be present they point toward a normal gestation. The writer states that we are taught that ectopic gestation enlarges the appendages of the uterus and that this can be made out by bimanual examination. A cystic corpus luteum will produce a temporary swelling which on bimanual examination might be taken for an unruptured ectopic pregnancy. The smoother the course of pregnancy the less importance should be placed on swelling of the appendages. Because the obstetrician cannot palpate a supposed gestation sac in a case of shock and pain he should not, therefore, conclude an ectopic pregnancy is not present. Many cases of ectopic pregnancy rupture gradually, with very little disturbance. The symptoms usually described apply best to cases of extensive and sudden rupture, but these do not comprise by any means all of ectopic pregnancy. There is a tendency to wait until air hunger or dulness in the flanks is present to complete the diagnosis of ectopic pregnancy and a dangerous condition of the patient. Emphasis should be placed upon the fact that the severity of the symptoms depends upon the quantity of blood lost more than upon the circumstance of rupture of the tube. Only small vessels are sometimes torn and the tear may be incomplete when the patient will have sudden pain, not very severe, followed by nausea and weakness. If the bleeding ceases the patient may soon feel as well as usual. When a considerable quantity of blood is lost the patient is usually pale, sweating, sometimes vomiting, and has a feeling of intense weakness. Air hunger and abdominal distention applying only to extensive and sudden hemorrhage. While there may be only very decided hemorrhage in the case, close questioning will bring out the fact that there has been a number of attacks of indefinite pain with some discharge. In any woman of child-bearing age seized with abdominal pain of severity, followed by shock or syncope, even though brief, the case must be regarded as a possible one of ectopic pregnancy until it can be proved to be otherwise. A blood count may assist in diagnosis. When the hemorrhage has been moderate the blood findings are not sufficiently characteristic to warrant a diagnosis of internal hemorrhage. As a leukocytosis is present the obstetrician may believe he is dealing with appendicitis. It is the rule that in ectopic pregnancy the leukocyte count is but little disturbed when the pregnancy is unruptured, After rupture there occurs a rapid increase in leukocytosis, and this becomes pronounced the larger the quantity of blood lost. A leukocytosis with a normal or subnormal temperature in a person who has had severe abdominal pain, followed by nausea and perhaps vomiting, should lead to a diagnosis of probable ruptured ectopic pregnancy. Emphasis

should also be laid upon the value of the exploratory vaginal incision in doubtful cases. This may make a diagnosis plain and justify immediate operation. Cases are sometimes sent to hospital where the condition is suspected but cannot be proved. These patients are repeatedly kept for observation, as the obstetrician is afraid to let them return to their homes. With such patients under observation a positive diagnosis should be made, and here vaginal incision is especially valuable.

GYNECOLOGY

UNDER THE CHARGE OF

JOHN G. CLARK, M.D.,

PROFESSOR OF GYNECOLOGY IN THE UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA,

AND

FRANK B. BLOCK, M.D.,

INSTRUCTOR IN GYNECOLOGY, MEDICAL SCHOOL, UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA.

Radium Treatment of Menorrhagia.—In the Mayo Clinic, according to STACY (*Amer. Jour. Roentgenology*, 1920, vii, 379), surgery is still the treatment of choice for young women who have definite fibroids causing menorrhagia, or for those who have a normal sized uterus but a history suggesting the presence of an intrauterine polyp or small submucous fibroid, and for those with a history suspicious of malignancy of the fundus of the uterus. They believe that the large fibroids are best treated by hysterectomy as a certain means of quickly removing the tumor, without the possibility of degenerative changes occurring later. It has been their policy to limit the use of radium to fibroids the size of a three and one-half to four months' pregnancy, unless there is a definite contra-indication to operation. A hysterectomy should be advised in the cases in which there is a history suggestive of malignancy, for a negative diagnostic curettement is not to be relied on in the definitely suspicious case, as the curette may miss the involved area. In the young woman who has a definite fibroid causing menorrhagia, an abdominal myomectomy is the preferable treatment. By this method the tumor is removed, the menorrhagia controlled and a uterus is preserved which is capable of carrying on the functions of menstruation and child-bearing. If a young woman has menorrhagia without a demonstrable tumor which cannot be controlled by medical treatment or by curettement, an abdominal hysterectomy may disclose a small submucous fibroid or polyp so situated that it could not be reached by the curette. In the series of 600 cases treated by radium, on which this report is based, 122 women were under thirty-five, while 19 were twenty-five or under. The average dose of radium given to these patients was 293 mg. hours. Menorrhagia was controlled by one treatment in 55 per cent. of the cases. In 25 cases the periods were reported normal in amount, in 11 irregular and scant and in 6 menstruation

ceased. They attempt to give the women under thirty-five enough radium to control the symptoms, but not enough to stop menstruation, and it is difficult to judge the amount necessary in each case. It is better to give a small dose, however, and if there is a recurrence of the profuse flow, repeat the dose in from three to six months than to give enough at the first treatment to stop menstruation. Patients over thirty-five are given larger initial doses, as it is not so important that menstruation shall continue, but they always try to give a dose to all patients under forty which will control rather than stop menstruation. They have seldom given more than 50 mg. for fourteen hours at one treatment, since they believe that it is better to repeat the treatment if necessary, as it is sometimes in cases of a fairly large tumor. In a series of 349 patients it was necessary to repeat the treatment in 64 and an operation was done later in 20. Only 4 of the 20 had been given a second radium treatment and two had operations elsewhere too soon after treatment to obtain the effect of the radium. Menstruation became regular and normal in 11 per cent.

Ovarian Therapy.—In the light of theoretic, experimental and anatomic knowledge combined with long-continued observations, our general estimate of the ovary as a gland of internal secretion has been briefly summarized by GRAVES (*New York Med. Jour.*, 1920, cxii, 697) as follows: For complete somatic growth and sexual development the normal secretion of the ovary is essential. To what extent the action of the secretion is direct and how far it serves as a balance to other more powerful secretory influences is a matter of speculation. During menstrual life, and especially during the years of adolescence, the proper functioning of the ovaries has a very important bearing on the physical and mental character of the individual. Disfunctions of the ovaries are usually attended with various neuroses. Some of these may be due to the direct disharmonious action of other endocrines, especially those that have an affinity for the autonomic nervous system. In the adult the ovarian secretion plays a somewhat minor role in the human economy, as is indicated by the comparatively slight physical changes that take place after ablation or the natural menopause. This has an important bearing on the question of removing the ovaries during hysterectomy. During adult life the most definite evidence of the existence of a true internal secretion from the ovaries is the occurrence of hot flushes and genital atrophy after ablation. These symptoms point to a balancing rather than a direct action of the ovarian secretion. From an organotherapeutic viewpoint the ovary must be regarded as primarily a homogeneous gland, the essential secreting structure being the interstitial cells. Variations in secretion of different parts of the gland are probably differences of degree rather than of kind. A selective action of the secretions from different parts of the gland is not yet proved, and if it exists is probably quantitative. The therapeutic value of ovarian preparations in Graves's experience may be stated somewhat as follows: All the ovarian preparations exert a specific influence on hot flushes. In this respect the residue is the most intensive, but the difference in the efficacy of the various preparations depends to some extent on the idiosyncracy of the patient. In the treatment of menstrual irregularities ovarian extracts exhibit an

undoubted specific action but this action is inconstant. In temporary functional amenorrhea, delayed menses, dribbling before and after catamenia and small clotting, ovarian therapy is fairly reliable, and is at least the best asset that the gynecologist at present possesses for these symptoms. Theoretically for these affections the ovarian action may be enhanced by the addition of thyroid and pituitary extract, but of this Graves's personal clinical experience has not been entirely convincing. For the permanent amenorrheas, especially those associated with pluri-glandular disturbances, ovarian therapy has little or no effect on restoring the menstrual function, but is of undoubted value in improving the patient's general health. It is best in these cases to administer the ovarian treatment in considerable doses, separately from the other gland extracts. In certain types of dysmenorrhea ovarian feeding is efficacious, occasionally brilliantly so, but it is unreliable and often disappointing after giving early promise. In the severe types of dysmenorrhea it is of comparatively little help. For menorrhagia and metrorrhagia ovarian therapy is not indicated.

Ovarian Transplantation.—There can be few gynecologists who have never had the experience of being obliged to open the abdomen at a longer or shorter period after a previous operation for salpingitis, because an ovary that had been left had become bound down with adhesions and was cystic. Encountering a number of these cases in his practice, BELL (*Lancet*, 1920, cxciv, 879) came to the conclusion that it is not worth while leaving an ovary in a badly infected area, when further conception is impossible owing to the frequency with which subsequent lesions occur. Some surgeons have solved this problem by frankly castrating the patient, but Bell has adopted the method of ovarian grafting. His first operation on the human subject was performed in 1912, but it was not until 1916 that he adopted the procedure as a routine practice in certain well-defined circumstances. The following points in regard to the technic of this precedure are important: All grafts in the human subject must be autoplastic. After the ovaries have been removed the ovarian tissue from which the graft is to be cut should be dropped to the bottom of the pouch of Douglas, where it will be kept warm and moist until the end of the operation, when it is required for grafting. When possible, healthy ovarian tissue, which may include all the elements of the organ, should be used. This should be criss-crossed with a sharp knife into adherent fragments after the dense tunica albuginea has been removed, in order to favor rapid vascularization of the grafted tissue. The graft, provided there is no suppurative infection of the ovary, may be placed in the rectus muscle before the laparotomy wound is closed. He has also implanted the graft in the uterus or in what was left of this organ. It is most important that the graft should be placed in a vascular site, but should not be surrounded with blood. Too much care cannot be taken in placing the graft among the muscle fibers. If the ovaries be badly infected and more or less completely converted into the walls of abscess cavities, whatever tissue can be removed should be implanted in the internal oblique muscle alongside the drainage tube, which in such circumstances is passed through a stab wound well away from the central incision into the pelvis. He has never seen an infected graft slough; moreover, in

several such cases menstruation has subsequently occurred. In only a few cases is menstruation regular after ovarian grafting. It usually recurs at longer intervals than normal—that is to say, every six weeks or two months. Some patients menstruate a few times and then cease and minor symptoms of the menopause may appear. Bell's conclusions, based on a fair experience, lead him to advocate very strongly the practice of ovarian grafting in suitable cases. Nevertheless, he insists that this procedure be looked upon as a measure of necessity, which can never be weighed in the balance against the preservation of the natural connections of the normal ovary.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

OSKAR KLOTZ, M.D., C.M.,

DIRECTOR OF THE PATHOLOGICAL LABORATORIES, SAO PAULO, BRAZIL,

AND

DEWAYNE G. RICHEY, B.S., M.D.,

ASSISTANT PROFESSOR OF PATHOLOGY, UNIVERSITY OF PITTSBURGH, PITTSBURGH, PA.

A Study of the Oxidase Reaction with A-Naphthol and Paraphenylendiamine Tumors.—The work reported by MENTEN (*Jour. Cancer Res.*, 1920, v, 321) consists in the application to tumor tissue of an oxidase technic previously studied in detail in various types of normal tissue. The reagent used was an aqueous solution of a-naphthol and paraphenylendiamine and when frozen sections of tumors were placed in this solution there developed within them a blue violet color whose intensity varied according to the type of tumor and the functional activity of its cells. While diverse types of neoplasms were studied the most striking results were obtained in fibrosarcomata where all gradations of color from a maximum in the degenerating areas to a faint reaction in the actively growing parts were met with. In the latter the color appeared only in the fine perinuclear granules which had a faint mauve appearance. The nucleus was free from any reaction. As the cell matured the reaction deepened to a violet in the perinuclear region and the chromatin was perceptible in the nucleus as faint mauve threads and knots. When through lack of adequate blood supply degenerative changes occurred in the cells the oxidase reaction became still further increased in the perinuclear granules and the nucleus and finally in the late stages of the degenerative process the whole cell protoplasm was converted into clumps of blue-black stained material. An attempt is made to interpret the phenomenon observed on a physicochemical basis. Since the development of the color is dependent upon the oxidation of the reagent and oxidation is due primarily to the acquisition of a positive electric charge it is postulated that any increase in the intensity of the color is due to the liberation of a positive charge within that tissue. That increased acidity occurs in degenerating tissues is a

well attested fact. The liberation of this positive charge within the cell is accompanied by conversion of potential into kinetic energy. In the actively growing parts where the oxidase reaction becomes progressively diminished, the reverse process occurs. It is assumed that it is those granules with high lability as manifested by wide variations in the oxidase reaction which most readily tend to become the primary site of metabolic changes of the nature of an anaplasia.

The Peroxide Reaction in Three Cases of Multiple Myeloma of the Bones with Remarks Concerning the Nosological Position of these Tumors.—Owing to the lack of definite knowledge concerning the origin of the cellular elements of multiple myeloma of the bones, a considerable confusion as to their proper classification has arisen. The various views which have been suggested as to the histogenesis of these rare tumors are fully discussed by MORSE (*Jour. Cancer. Res.*, 1920, v, 345) who has studied three cases, the autopsy findings of which are reported in detail. The gross appearance of these new growths is very characteristic. They arise in the bone marrow by multiple foci whose extension causes marked erosion of the bone. There is little or no tendency to callus formation or reparative processes. Metastases occurred in one of the cases reported by Morse. Microscopically the tumors are composed of cells irregularly oval in outline and contain an eccentrically placed nucleus. The nucleus is vesicular and shows a characteristic mural arrangement of the chromatin. The protoplasm is basophilic. Because of the close resemblance morphologically of these cells to the plasma cell and further because they react negatively to both Goodpasture's and Evan's oxidase technic, Morse concludes that they are not of myeloblastic origin and have no relationship to the leukemic group, but that "they spring from a series of cells whose specific function is bone absorption." It is suggested that they are related to the osteoblast and may be considered as heteroplastic osteoblasts.

The Biliary Factor in Liver Lesions.—ROUS and LARIMORE (*Jour. Exp. Med.*, 1920, xxxii, 249) attempted to arrive at a better understanding of the share of bile in the causation of hepatic lesions distinguished by a cirrhosis with evidence of stasis in the finer bile ducts and inflammation in their walls, by producing in rabbits obstruction to the bile flow at different levels. The authors confirmed the work of previous investigation in producing bile stained parenchymal necrosis after obstruction of the common duct, which was followed by a spreading stellate cirrhosis and connective-tissue proliferation throughout Glisson's capsule, resulting finally in a roughly hob-nailed organ. This rabbit lesion is mixed, involving injury throughout the biliary tract. By causing local obstruction at different duct levels, the authors attempted to produce cirrhoses of uncomplicated types, resembling lesions in man. The bile duct and portal branch to the main liver mass of rabbits were ligated. There was found to result atrophy of the lobule and an evenly distributed monolobular cirrhosis. When the portal trunk of the main liver mass was ligated and seventeen to twenty-three days later the bile duct from this region was ligated, the main liver mass was found to have undergone atrophy. There was no icteric tinting of the parenchyma or dilatation of the bile passages. Evidently a very slight increase of

pressure within the ducts checked secretion into the normal channels. Yet, when the material for bile formation is provided in unusual quantity, by injecting hemolytic serum intravenously, a parenchyma deprived of portal blood can secrete bile into the ligated duct under considerable pressure. Intralobular stasis, and its corollary intralobular cirrhosis, can be brought about in the liver of rabbits by diverting the whole portal stream and ligating the efferent duct. When the duct from the main liver is also tied, the secretory activities of the lobe become strikingly evident, the lobules showing intense bile staining and intralobular cirrhosis developed rapidly without necrosis, as the increased portal flow provides a circulation to cells that otherwise would have been deprived of it. The authors conclude that the principles illustrated in their experiments may be applied to the biliary lesions of man, though the picture in man is varied by the fact that human bile is relatively non-irritant, that infection occurs more frequently in areas of stasis, and the liver parenchyma responds but slowly to deranged circulatory conditions. It is the belief of the authors that the diversity of the liver changes in man depend upon the duct levels at which the injurious agent is active, and that bile stasis may complicate any chronic liver derangement in which the bile passages are compromised.

A Rapid Method of Pneumococcus Typing.—Because of its value in prognosis and for specific serum therapy several methods for the determination of pneumococcus types have been devised. OLIVER (*Jour. Infect. Dis.*, 1920, xxvii, 310) employs a procedure based on the solubility of the pneumococcus in bile. The relative number of pneumococci is determined by a direct smear of the sputum stained by Gram's method. To one and one-half c.c. of sputum is added a sufficient quantity of normal salt solution to insure a homogeneous specimen which can be filtered or centrifugalized and the mixture is thoroughly stirred with a glass rod. From 3 to 5 drops of undiluted ox bile are then mixed with the diluted sputum, which is then heated to 45 to 48° for ten to twenty minutes in a water-bath. The fluid is then filtered or centrifugalized. Of the filtrate or centrifugate, 0.3 to 0.5 c.c. are pipetted into each of three small tubes. To the first tube is added one drop of undiluted type one pneumococcus antiserum, to the second, one drop of type two antiserum and to the third tube an equal quantity of type three antiserum. A positive precipitin test consist of a clouding which is enhanced by heating to 40° C. for ten to twenty minutes. If then placed in the ice-box for several hours the positive tube will show sedimentation. The method was used on 25 cases. In all of those where a positive precipitin test for one of the first three types of pneumococci was obtained, the results were identical with those obtained by the Avery method. In the 15 cases in which the rapid precipitin test was negative, the Avery method revealed a type four pneumococcus in 11 and streptococcus in 4. Of these 15 cases, intraperitoneal inoculation of mice with washed sputum was employed in 10, and each time the result was the same as in the Avery method. The author suggests the subsequent use of the mouse on those sputa in which the rapid precipitin test fails to reveal a type.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

MILTON J. ROSENAU, M.D.,

PROFESSOR OF PREVENTIVE MEDICINE AND HYGIENE, HARVARD MEDICAL SCHOOL, BOSTON, MASSACHUSETTS,

AND

GEORGE W. McCOY, M.D.,

DIRECTOR OF HYGIENIC LABORATORY, UNITED STATES PUBLIC HEALTH SERVICE, WASHINGTON, D. C.

Masked Juvenile Tuberculosis.—COOKE and HEMPELMANN (*Am. Rev. Tubere.*, November, 1920, iv, 660) believe that masked juvenile tuberculosis presents a sufficiently distinctive clinical type to deserve a prominent place in the category of tuberculous affections in childhood. They state that the characteristic clinical picture may be briefly sketched as follows: a history of frequent coughs and colds, with or without known exposure to tuberculosis, attacks of unexplained fever, often with afternoon elevations, anorexia, loss of weight and asthenia. On physical examination, there is found more or less malnutrition, occasionally anemia, and chest signs referable to enlarged tracheobronchial nodes. In certain instances there may be in addition phlyctenular disease or skin tuberculides. The Pirquet or intracutaneous tuberculin tests are positive, and, in those over four years of age, three-fourths of the children give a positive complement-fixation text for tuberculosis. The chest findings may be verified by the use of the roentgen ray which not infrequently reveals unsuspected lesions of varying size and age in the lung parenchyma as well. The diagnosis must of course rest not in any *one* of the points mentioned, but rather upon a review of all the findings; and there the authors wish to emphasize the value of the complement-fixation test in calling attention to this class of cases.

Saliva-borne Infections: Their Transmission through Eating Utensils.—CUMMING, SPRUIT and REUTER (*Mod. Med.*, July, 1920, No. 7, ii) conclude as follows from their investigations on saliva-borne infections: First and foremost in the control of the saliva-borne infections is a reduction in the transmission rate. This will diminish the large mass of carriers, who are far more important as sources of distribution for this group of infections than the actual cases in the hospital. Further attempts should be made to determine with accuracy the major and minor routes of transmission and the several links in the chain of these routes. The authors conclude from their studies that it appears eating utensils rank foremost as transmitting agents of the saliva-borne infections. These utensils either enter the mouth or touch the lips; they become contaminated with organisms of the oral cavity; they are still contaminated after they are hand washed, and the next user acquires this contamination. The use of utensils contaminated with organisms of one or more of the saliva-borne diseases does not necessarily mean infection, but this major avenue of transmission is so prolific and so

universal that a large number of saliva-borne infections occur and cause more deaths than all other groups combined. There is no avenue of indirect transmission more frequent than through insanitary eating utensils. We eat three time a day with utensils previously used by others; these utensils are not rendered aseptic; they actually enter the mouth—the normal portal of entry of the saliva-borne infections, and preventive measures must take them into account. The greatest hope for the control of this group of infections, especially tuberculosis and the fatal secondary pneumonias, lies in the universal practice of eating-utensil pasteurization by the use of boiling water. This applies alike to the home and the public eating place. In the home, eating utensils should be scalded before they are washed; in the public eating places they should be scalded in the process of mechanical washing. In public eating places this procedure of cleansing is not only economical, but its value as a public health measure in eliminating the primary center of saliva-borne disease distribution should be recognized.

Fatigue and Efficiency of Smokers in a Strenuous Mental Occupation.—BAUMBERGER and MARTIN (*Jour. Indust. Hyg.*, 1920, ii, 207) report the results of an investigation of the industrial efficiency of persons using tobacco in different amounts. Many studies have been made of the effects of tobacco on the human body, but probably no industrial output study of smokers and non-smokers has been reported hitherto. The authors state that if the data on which they base their conclusions are representative, two respects in which heavy smokers fail to maintain the level set by light smokers in a strenuous mental industrial occupation are established; namely, in a lessened ability to sustain output to the end of the working day, and in a diminished power to react by increased effort to an increase in the volume of business. They indicate, also, in favor of heavy smokers, a better output during the first hours, although this does not amount nearly to enough to compensate for the lowering of efficiency toward the close of the day. On the whole, they constitute an argument in favor of moderation in the use of tobacco on the part of industrial workers whose tasks fall in the category here under discussion. This conclusion is in line with the findings of various investigators of the records of college students and also football players: that extensive use of tobacco goes hand in hand with relatively low scholarship. It is probable, moreover, that no class of men is oftener advised by physicians to use moderation in consumption of tobacco than that made up of business executives, men who habitually do mental work under tension. All these facts are in line with the conclusion that strenuous mental work is likely to be affected adversely by heavy smoking.

Notice to Contributors.—All communications intended for insertion in the Original Department of this JOURNAL are received only *with the distinct understanding that they are contributed enclusively to this* JOURNAL

Contributions from abroad written in a foreign language, if on examination they are found desirable for this JOURNAL, will be translated at its expense.

A limited number of reprints in pamphlet form, if desired, will be furnished to authors,*providing the request for them be written on the manuscript.*

All communications should be addressed to—

DR. GEORGE MORRIS PIERSOL, 1913 Spruce St., Philadelphia, Pa., U. S. A.

Your Most Difficult Diabetic—

The one hardest to hold to the diet, the nervous, irritable, discouraged one; the one whose hunger is never satisfied; these are the cases which will amply demonstrate the value of Listers Diabetic Flour.

When Listers Flour is used the word "diet" loses its dread meaning. The nervous patient is braced and strengthened; irritability is overcome; the discouraged one sees life from a more cheerful standpoint.

LISTERS DIABETIC FLOUR

(PREPARED CASEIN)

Strictly Non-carbohydrate

The use of Listers Flour largely discounts the terrors of meal-time, and provides satisfying and palatable foods for the most exacting patient. Listers Flour is made from prepared casein and is entirely free from starch and sugar.

It makes food that *tastes* good.

SELF-RISING. Packed in small, carefully weighed boxes—each containing the correct protein-content, per day, for the average patient—and accompanied by carefully tested recipes for making

BREAD, MUFFINS, PASTRY

All palatable and easily made in any home

A Month's Supply (30 boxes) **$4.85** **Fifteen Days' Supply** (15 boxes) **$2.75**

Will be sent direct to the physician or to his patient.
Or write us for name of our Agent in your locality

LISTER BROS., INC., 405 Lexington Ave., New York City

Antirheumatics and Analgesics

Internally **NOVASPIRIN or SALOPHEN** Internally

Especially adapted for children and delicate persons and where an intense salicyl effect is not required.

Externally **MESOTAN** Externally

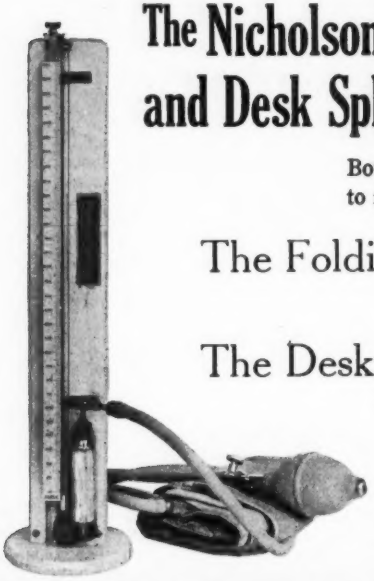
Rapidly penetrates the skin and produces a salicylic acid action upon the affected tissues as well as a derivative effect. An efficient auxiliary to internal medication.

HOW SUPPLIED: **Novaspirin** and **Salophen**: 5 gr. tablets, bottles of 25 and 100. Powder in ounces.
Mesotan: In ounce bottles.

Literature on Request

WINTHROP CHEMICAL COMPANY, Inc.
189-191 Franklin Street, New York, N. Y.

The Nicholson Princo Mercurial Folding and Desk Sphygmomanometers



Both graduated to 300 mm., and easily adjusted to zero reading

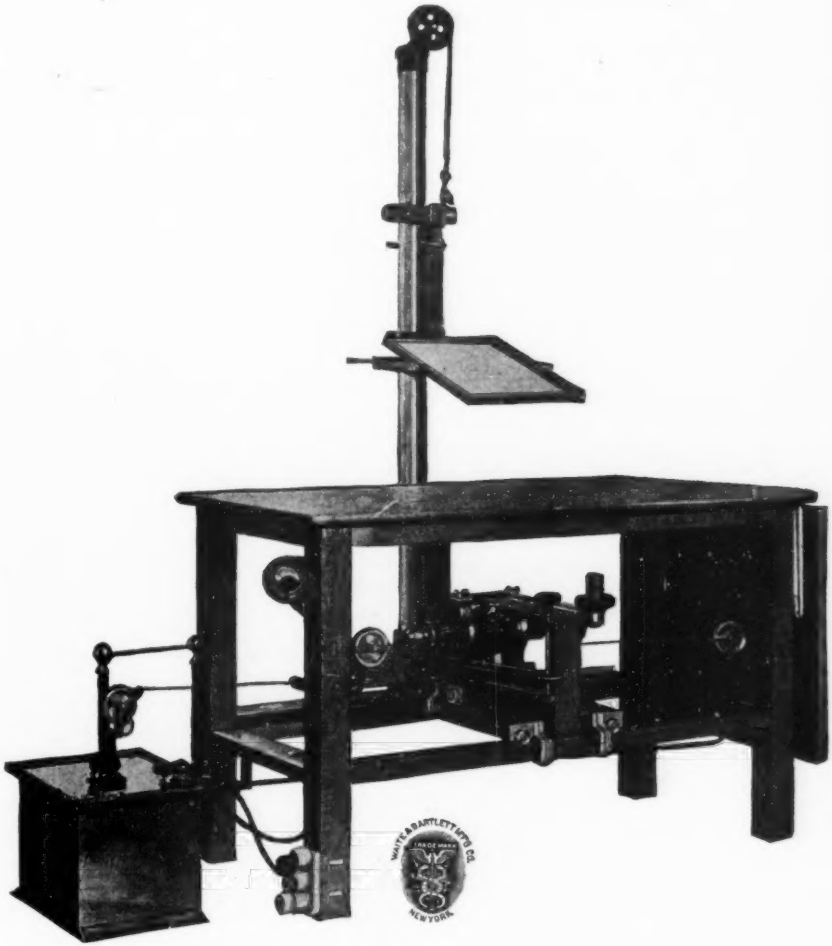
The Folding Instrument $30.00
Type "B"

The Desk Instrument $25.00
In White Enamel

Our booklet entitled "Blood Pressure" and a pamphlet on "The Clinical Significance of Diastolic and Pulse Pressure" by Percival Nicholson, M.D., will be cheerfully mailed upon request

PRECISION THERMOMETER & INSTRUMENT CO. **1434 Brandywine St. Philadelphia, Pa.**

HORIZONTAL TABLE AND THE U. S. ARMY BEDSIDE TRANSFORMER



WAITE & BARTLETT MFG. CO.

53 JACKSON AVENUE, LONG ISLAND CITY, N. Y.

Showroom: 103 PARK AVENUE, NEW YORK CITY

California Agents: Gagan-Richardson Co., 127 E. 6th St., Los Angeles, California

Adrenalin in Medicine

6—In Endocrinology

THE action of Adrenalin is so fleeting as to narrow the scope of its utility in organotherapy. Its important place in clinical endocrinology is that of a diagnostic indicator of deviations from the normal secretory activity of certain glands.

Hyperthyroidism can be detected by the Goetsch test. This test is based on the fact that thyroid secretion sensitizes the sympathetic nerve endings to the action of Adrenalin. The technique consists of the subcutaneous injection of 0.5 cc Adrenalin 1:1000 and the subsequent observation of objective and subjective phenomena.

Blood-pressure readings are taken over a period of one and one-half hours at intervals varying from two and one-half minutes at the beginning of the reaction to ten minutes at the end. In positive cases the systolic blood-pressure rises at least ten points during the first fifteen minutes with an accompanying increase of about ten beats a minute in the pulse-rate. Soon there is noted a slight fall in systolic pressure and then a secondary rise. In about ninety minutes the blood-pressure is back to normal.

The subjective symptoms are sometimes striking. There are heart consciousness, apprehension, and marked tremor and pallor occasionally followed by flushing and sweating. The greatest diagnostic importance of the Goetsch test is in distinguishing cases of mild hyperthyroidism from those of incipient tuberculosis.

A satisfactory test for suprarenal function can be performed by injecting subcutaneously fifteen to twenty minims of Adrenalin 1:1000 and estimating the consequent variations in blood sugar. In cases of suprarenal irritability there is an increase in blood sugar which comes on in about thirty minutes and lasts for several hours. A transient glycosuria may likewise be noted.

Loewi's test for pancreatic diabetes is dependent upon the fact that the suprarenal glands and the pancreas are physiological antagonists. In pancreatic diabetes there is impairment if not destruction of the secretory cells which allows certain Adrenalin effects to be more pronounced. One or two drops of Adrenalin 1:1000 should be instilled into one eye. In positive cases—cases of pancreatic insufficiency—there will be a prompt dilatation of the pupil.

PARKE, DAVIS & COMPANY

AN IDEAL ARSENICAL

SODIUM DIARSENOL

SODIUM ARSPHENAMINE

SODIUM DIARSENOL marks a distinct advance in syphilology. It dissolves very quickly in water, giving a solution ready for immediate injection. No addition of sodium hydroxide is necessary. It has the therapeutic advantage of arsphenamine with the solubility and convenience of neoarsphenamine, and gives clinical results equal to or better than either of the two latter compounds. Neutralization with alkali being obviated, there is no undue handling and consequent decomposition of the highly reactive solution.

SODIUM DIARSENOL has been accepted by the council on Pharmacy and Chemistry of the American Medical Association for inclusion in "New and Nonofficial Remedies."

Manufactured by Diarsenol Laboratories, Inc., Buffalo, N. Y., under license from The Chemical Foundation, Inc., under patents 1059983 and 1078135.

Samples and literature on request

DIARSENOL COMPANY

INCORPORATED

BUFFALO BOSTON ATLANTA

International Congress

— of —

Military Medicine and Pharmacy

THE Medical Corps of the Belgian Army is organizing in Brussels for the month of June, 1921, an International Congress of Military Medicine and Pharmacy, to which are invited all the doctors and pharmacists belonging or having belonged to the armies of the allied and neutral countries.

At the close of the great events which have involved the nations from 1914 to 1918, it is interesting to co-ordinate the work of the different medical departments, and to compare, for the purpose of reciprocal benefit, the different results obtained; it is also useful to note the advances of military medicine during the war so as to be able to condense them into lessons for future use.

The following questions have been selected for the order of the day:

First. The experiences of the war in the treatment of fractures of the limbs.

Second. Antivenereal and antituberculous campaigns in the army.

Third. A chemical and physiological study of war gases. The consequences of their action on the organism. The importance of these consequences in the prognosis of gas cases.

Fourth. The general organization of the medical departments of the armies.

Communications to the Congress, as well as the articles and reports concerning the different questions, must be sent by the first of April, 1921, to the GENERAL SECRETARY OF THE CONGRESS, DOCTEUR JULES VONCKEN, HÔPITAL MILITAIRE DE LIEGE, BELGIUM. The articles must be accompanied by a brief summary.

A remarkably efficacious remedy in furunculosis

The curative effects of yeast described by physicians and physiological chemists

The successful use of yeast in certain maladies has been demonstrated by careful tests. In leading institutions in New York and Philadelphia the yeast treatment was given in 17 cases of furunculosis.

The tests were carried on under the direction of Philip B. Hawk, Ph.D., by Frank Crozer Knowles, M. D., Martin E. Rehfuss, M. D., and James A. Clarke, M. D., with the collaboration of Olaf Bergeim, Ph.D., H. Rodell Fishback, M. D., Sc.D., Clarence A. Smith, Ph.D., and Robert A. Lichtenthaeler, M. S.

The cases covered such conditions as single large boil; boils a week apart for two months; and periodic boils for years. One patient had several large boils which did not yield to vaccine. After three cakes of yeast daily for two weeks the boils disappeared. A boil started on the leg after yeast was stopped. The yeast treatment was resumed. The boil soon cured.

Fleischmann's Yeast was used throughout the investigation—as being not only the most readily available, but also because it gave assurance of absolute uniformity and purity.

The conclusion of Dr. Philip B. Hawk and his associates is: "In furunculosis, yeast is a remarkably efficacious remedy. Its curative action in these cases is no doubt aided by the leukocytosis which is developed."

The usual dosage in these cases was three cakes a day—suspended in water, beef-tea, or orange juice—generally before meals. In some cases, because of the laxative action of the yeast, it was necessary to reduce the dosage.

With patients troubled with gas formation, it was found preferable either to administer yeast between meals, or else to "kill" the yeast by placing it in boiling water for a few minutes. The action of the "killed" yeast proved to be much the same as that of the living yeast.

A full report of this test can be found in the Journal of the A. M. A. for October 13, 1917, under the title: "The Use of Baker's Yeast in Diseases of the Skin and of the Gastro-Intestinal Tract."

Fleischmann's Yeast may be obtained fresh daily from all grocers. Physicians may write to The Fleischmann Company in the nearest large city and a supply will be mailed direct on the days wanted.

THE FLEISCHMANN COMPANY

701 Washington Street New York, N. Y.
941 Mission Street San Francisco, Cal.
327 South La Salle Street Chicago, Ill.
508 Greene Building Seattle, Wash.
208 Simcoe Street Toronto, Canada

We are now manufacturing

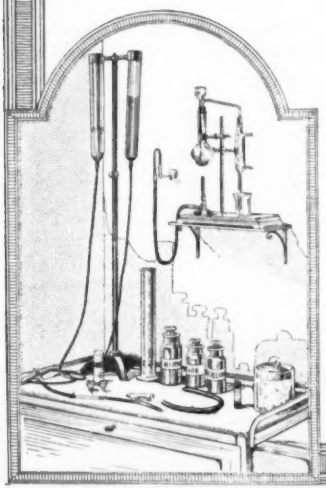
SILVER-SALVARSAN

(The sodium salt of silver-diamino-dihydroxy-arsenobenzene)

This has been used with success in Europe for more than two years past. Silver-Salvarsan is in clinical use in the following New York hospitals and clinics:

Vanderbilt Clinic .	(Service of Dr. Fordyce)
Skin and Cancer .	(Service of Dr. Stetson)
Bellevue . . .	(Service of Dr. Parounagian)
Volunteer . . .	(Service of Dr. Bake el)

The physicians who are administering the product are well satisfied with the results obtained. Silver-Salvarsan effects a more rapid disappearance of the contagious legions than the other forms of Salvarsan, and practically no reactions follow its administration.



SILVER-SALVARSAN

will be ready on March 1, 1921, for general distribution to the medical profession.

HA
M E
T Z
LAB

TRADE MARK REG. U. S. PAT. OFF.

HA-METZ LABORATORIES, Inc.
One-Twenty-Two Hudson Street, New York.

Palatable

Benzyl Benzoate 20%

AROMATIZED SUSPENSION

(Made from VAN DYK & CO. brand)

Jour. Am. Med. As., Oct. 16, 1920, Page 1069

Antispasmodic in ASTHMA and DYSMENORRHEA

OUR SUSPENSION IS PREFERABLE because it is:

NON-ALCOHOLIC

READILY MISCIBLE with WATER

RARELY REGURGITATES

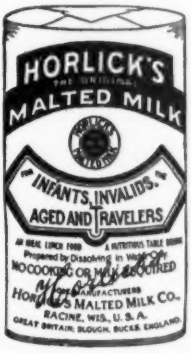
PLEASANT to the EYE

Write for Clinical Data

United Synthetic Chemical Corporation

4 Platt Street **New York, N. Y.**

AVOID IMITATIONS


HORLICK'S
MALTED MILK
FOR INFANTS, INVALIDS, THE AGED AND TRAVELERS
NO COOKING OR MILK REQUIRED
HORLICK'S MALTED MILK CO.
RACINE, WIS., U. S. A.
GREAT BRITAIN: SLOUGH, BUCKS, ENGLAND

PRESCRIBE THE ORIGINAL PRODUCT OF RELIABLE QUALITY

Virginia Hot Springs

Open All Year Round

WINTER days at this great American Spa are most pleasant and beneficial. Its "cure" provides every variety of scientific bath and hydrotherapeutic treatment. Natural waters of recognized potency work wonders, assisted by massage, Swedish gymnastics and the latest mechanical apparatus for corrective exercises.

AN enclosed viaduct leads from hotel to bath house. The luxurious Homestead—2500 feet up in the Alleghanies—enjoys a Winter climate both mild and bracing. Sheltered, sunlit piazzas invite complete relaxation. Every facility for sport outdoors, every comfort and convenience within. Tempting Southern cuisine.

Interesting and Informing Brochures on Request

THE HOMESTEAD

CHRISTIAN S. ANDERSEN, Resident Manager — **Hot Springs, Va.**

NEW YORK BOOKING OFFICE—THE RITZ-CARLTON

Experimental Pharmacology

By HUGH McGUIGAN, Ph.D., M.D.

Professor of Pharmacology, University of Illinois, College of Medicine, Chicago

Octavo, 251 pages with 56 engravings and 7 colored plates (mostly original) Cloth, $3.00, net

THIS manual presents experimental pharmacology in a brief, concise form but gives an adequate view of the field. It follows and illustrates the most important part of the text-book work. Sufficient experiments are given to demonstrate the chief actions of each drug. It discusses Mode of Pharmacological Action, Results of Drug Action, Chemical Composition, Conditions Modifying Effects of Drugs, Technic, Anesthesia, Insufflation, Antiseptics and Disinfectants; Paralysis of Motor Nerve Endings; Autonomic System and Autonomic Drugs; Antagonism; Antipyretics; General Protoplasm Poisons; and the PHARMACOLOGY of—Gastro-Intestinal Tract—of Cranial Nerves—of Heart and Blood Pressure—of Sensory Nerve Ends—the Eye—the Glands—the Kidneys—Sweat Glands—Liver, Mammary Glands, Uterus and Bladder—the Muscles—the Lymphatics—of the Blood, etc.

LEA & FEBIGER

PHILADELPHIA 706-10 Sansom St. — NEW YORK 2 W. 45th St.

Principles and Practice of Surgery — Ashhurst

New (2nd) Edition

MUCH new matter has been introduced, some sections have been entirely rewritten, and all portions of the volume have been thoroughly revised and brought up to date. These additions have added about sixty pages to the volume, in spite of continued efforts at conciseness of expression and omission of the unessential.

THE growing importance of Reconstructive Surgery caused the author to collate all material on the subject in an entirely new chapter. The chapter on Gunshot Wounds has been entirely rewritten, as have also the sections in other chapters dealing with Shock, Infected Wounds, Carcinoma of the Tongue, Empyema, Typhoid Carriers and Surgery of the Pancreas.

SEVEN new colored plates and over one hundred new illustrations have been inserted. Most of the new skiagraphs are from the writer's services at the Episcopal and Orthopædic Hospitals and from the Walter Reed General Hospital. The photographs illustrating the Carrel-Dakin method of wound treatment are from the latter hospital. The work is divided into three parts. Nine chapters are devoted to General Surgery, seven chapters to Systemic Surgery, and thirteen chapters to Regional Surgery. Students and practitioners alike will find this text of immensely practical value.

By ASTLEY P. C. ASHHURST, A.B., M.D., F.A.C.S., Associate in Surgery, University of Pennsylvania; Surgeon to the Episcopal Hospital and to the Philadelphia Orthopædic Hospital and Infirmary for Nervous Diseases; Colonel, Medical Reserve Corps, United States Army. Octavo, 1202 pages, with 14 colored plates and 1129 illustrations in the text, mostly original. Cloth, $10.00, net.

New (2d) Edition

Thompson on Syphilis

THE work is devoted chiefly to diagnosis and treatment. Under clinical diagnosis you get detailed and thorough consideration of the chancre, lymphatic glands, cutaneous lesions, syphilis of the appendages of the skin, mucous membranes and general symptoms. The chapter on laboratory diagnosis is made especially full since the necessity of laboratory aid is more evident for the successful treatment of syphilis than any other disease. This includes collection of material, dark-field illumination, staining, complete details on the Wassermann and other modifications of this test, including Noguchi's, Hecht-Weinberg, Thompson's, other serological tests, and the Cerebrospinal Fluid and its examination, etc.

Treatment includes general treatment—specific treatment—mercury, the arsenics, iodin, with the various methods of administration and remarks on their comparative values—symptomatic and special treatment. Then follow fourteen exhaustive chapters on Regional Syphilis and Congenital Syphilis where again, Prognosis, Diagnosis, Prophylaxis and Treatment are covered.

Since the appearance of the first edition the author has been particularly impressed with the importance of Visceral Syphilis. Consequently, after carefully reviewing the literature, he has practically rewritten the sections dealing with it. All new material of importance has been added and certain sections, for example that on Syphilodermata, have been amplified. The author emphasizes the practical clinical aspects of the subjects under discussion. Only those methods of diagnosis and treatment which have proved to be useful and efficient are included. Illustrations, to a large extent, are from photographs taken by the author.

By LOYD THOMPSON, M.D., Physician to the Syphilis Clinic, Government Free Bath House; Visiting Urologist to St. Joseph's Hospital; Consulting Pathologist to the Leo N. Levy Memorial Hospital, Hot Springs, Arkansas; Lieutenant-Colonel, Medical Corps, U. S. Army, etc. Octavo, 486 pages, with 81 engravings; and 7 colored plates. Cloth, $7.00 net.

706-8-10 Sansom St. PHILADELPHIA

LEA & FEBIGER
PUBLISHERS

2 W. 45th Street NEW YORK

New (2d) Edition

Nutrition and Clinical Dietetics

CARTER, HOWE and MASON

IN Parts I and II (*Foods and Normal Nutrition*) there has been made an adequate revision of the chapters on Energy, Metabolism and Digestion, particularly with regard to the physiology of digestion; also an *entire* revision of the chapter on Vitamines, and as well a new chapter on Metabolism in Pregnancy and Lactation together with the Feeding of Children over Two Years Old.

In Part III (*Feeding in Infancy and Childhood*) there has been a general overhauling of the material in the light of the more recent literature. To Part IV (*Feeding in Disease*) there has been added some fifty pages of new material gathered from a careful review of the subject of Dietetics in Disease as found in the publications of the past three years.

By HERBERT S. CARTER, M.D., Assistant Professor of Clinical Medicine, Columbia University; Consulting Physician to the Lincoln Hospital, New York; PAUL E. HOWE, M.A., PH.D., Associate in Animal Pathology, Rockefeller Institute; Assistant Professor of Biological Chemistry, Columbia University; Officer in charge of Laboratory of Nutrition, Army Medical School, Washington, D. C., and HOWARD H. MASON, A.B., M.D., Instructor in Diseases of Children, Columbia University; Associate Attending Physician to the Presbyterian Hospital, New York. *Octavo, 703 pages, illustrated.* *Cloth, $7.50, net*

Principles of Biochemistry

DAILY more and more importance is being attached to Biochemistry. In the practice of medicine the advances of biochemical knowledge and technic are furnishing the physician with diagnostic methods of precision and indications for treatment based upon exact knowledge. In this work Biochemistry is represented in close relationship to physiology, so that the student may perceive the intimate dependence of these two sciences and come to regard physiological chemistry as the foundation upon which we must ultimately build our interpretations of the functions of living matter.

The book contains a full discussion of nutrition, basal metabolism, endogenous and exogenous metabolism, hydrogen-ion concentration, ductless glands, acidosis, blood-pressure, vitamines, anaphylactic shock, diabetes, chemistry of respiration, temperature effects, osmotic pressure, cholesterol, creatinine, etc. Tables and formulæ abound throughout the work, standard tests and reactions are given and methods and apparatus are clearly described and illustrated.

Emphasis has been placed upon the *practical applications* of the subject, and not only to the practice of medicine, but also upon the applications to the industries and to general biology. Thus, this text-book is not only for medical students and students specializing in biochemistry and physiology, but for the agricultural student, the student of general biology or the industrial chemist engaged in handling biological products.

BY T. BRAILSFORD ROBERTSON, PH.D., D.Sc., Professor of Physiology and Biochemistry, University of Adelaide, South Australia; Formerly Professor of Biochemistry, University of Toronto; Professor of Biochemistry and Pharmacology, University of California. Octavo, 633 pages, with 49 engravings. Cloth, $8.00, net.

706-8-10 Sansom St. PHILADELPHIA

LEA & FEBIGER

PUBLISHERS

2 W. 45th Street NEW YORK

Volume I Now Ready. Volume II, Shortly

Surgical Diagnosis and Treatment

BY EMINENT SURGICAL AUTHORITIES

EDITED BY

ALBERT J. OCHSNER, M.D., F.A.C.S.

Professor of Surgery in the University of Illinois; Surgeon-in-Chief to the Augustana and St. Mary's Hospitals, Chicago, Ill.

Four octavo volumes of about 850 pages each, with over 2000 illustrations, many in colors. Cloth, per set, $40.00, net; in Canada, $45.00, net

"THE GREATEST SURGERY OF ALL TIME"

is what we believe you will call this work, for seventy-six of America's greatest surgeons have written it.

It in every sense *reflects the current practice and thought of the most intensely active surgeons of this continent.* Its chapters tell the *why* and *how* in the solution of each surgical problem, *what to do and what to avoid.* It brings you in touch with the *actual experience, reasoning and practical methods* of men eminent in all parts of the country. Each one describes intimately his methods of diagnosis, his plans for treatment before and after operation and gives his judgment regarding them. This monumental work gives you the opinions *not of one man,* but the *combined experience, skill and advice of seventy-six of our foremost surgeons.*

Each man writes on the field in which he has achieved greatest success and fame

You will find nothing here that smacks of what is copied from text-books; but only fresh material that represents the living work of today done by those who are the outstanding surgical authorities of the country. The illustrations are almost, if not quite, as important as the text, so illuminating are they. Time and time again you will find *whole series devoted to the detailed disclosure of each step of a particular operation.* The technique of difficult procedures is made wonderfully clear and easily grasped through these admirable illustrations. Thoroughness is the keynote of the entire work. No expense or pains have been spared in its preparation. Proofs have been revised and again revised to insure smoothness of diction and the inclusion of all up-to-date material up to the very minute of going to press. Destined to be the Standard American Authority on Surgery, this work should find a place in the library of every Practitioner, Specialist and Surgeon for its value in daily use and as *THE* authoritative reference.

(*See Opposite Page*)

706-8-10 Sansom St. PHILADELPHIA

LEA & FEBIGER

PUBLISHERS

2 W. 45th Street NEW YORK

THE EMINENT CONTRIBUTORS

(*See Opposite Page*)

ABBE, ROBERT, M.D.
ALBEE, FRED H., M.D., F.A.C.S.
ANDREWS, E. WYLLYS, A.M., M.D.
ARCHIBALD, ALEXANDER, M.D., CH.B. (EDIN.).
ARMSTRONG, GEORGE E., M.D., F.A.C.S.
ASHHURST, ASTLEY P. C., M.D., F.A.C.S.

BECK, CARL, M.D., F.A.C.S.
BECK, EMIL G., M.D., F.A.C.S.
BECK, JOSEPH C., M.D., F.A.C.S.
BINNIE, JOHN FAIRBAIRN, F.A.C.S.
BOTTOMLEY, JOHN TAYLOR, M.D., LL.D.
BRADFORD, E. H., M.D., F.A.C.S.
BRAASCH, W. F., B.S., M.D.
BREWER, GEORGE EMERSON, M.D., LL.D.
BROWN, GEORGE VAN INGEN, M.D., F.A.C.S.
BRUCE, HERBERT A., M.D., F.R.C.S., ENG.
BUERGER, LEO, M.D., M.A., F.A.C.S.

CLARK, JOHN G., M.D.
CRILE, DENNIS W., B.S., M.D.
CRILE, GEORGE W., M.D., F.A.C.S.
CUNNINGHAM, JOHN H., M.D.
CUSHING, HARVEY, M.D., SCD., F.R.C.S.

DA COSTA, JOHN CHALMERS, M.D., LL.D.
DAVIS, CARL B., M.D.
DEAVER, JOHN B., M.D.

ESTES, WILLIAM L., M.A., M.D.
ESTES, WILLIAM L., JR., B.A., M.D.

FAY, OLIVER J., S.B., M.D., F.A.C.S.
FINNEY, J. M. T., M.D.
FREEMAN, LEONARD, M.D.

GIBBON, JOHN H., M.D.
GREENOUGH, ROBERT B., M.D.

HAGGARD, WILLIAM D., M.D., F.A.C.S.

JACKSON, CHEVALIER, M.D.
JONAS, A. F., M.D.

KAHLKE, CHARLES EDWIN, M.D., F.A.C.S.
KANAVEL, ALLEN B., M.D.

LEWIS, DEAN, M.D.
LILIENTHAL, HOWARD, M.D., F.A.C.S.

MCKECHNIE, ROBERT E., M.D., F.A.C.S.
MCLEAN, ANGUS, M.D., F.A.C.S.
MCWILLIAMS, CLARENCE A., M.D., F.A.C.S.
MACCARTY, WILLIAM CARPENTER, M.D.
MACKENZIE, KENNETH A. J., M.D., F.A.C.S.
MACLAREN, ARCHIBALD, M.D., F.A.C.S.

MARTIN, FRANKLIN H., M.D., F.A.C.S.
MATAS, RUDOLPH, M.D., F.A.C.S.
MAYO, WILLIAM J., M.D., F.A.C.S.
MEYER, WILLY, M.D.
MURPHY, FRED T., M.D.

NADEAU, OSCAR E., B.S., M.D.
NUZUM, JOHN W., S.B., M.D.

OCHSNER, ALBERT J., M.D., F.A.C.S.

PERCY, NELSON MORTIMER, M.D., F.A.C.S.
PFEIFFER, DAMON B., M.D.
PILCHER, JAMES TAFT, M.D.
PILCHER, LEWIS STEPHEN, M.D., LL.D.
POLLOCK, LEWIS J., M.D.
POWERS, CHARLES A., A.M., M.D.
PUSEY, WILLIAM ALLEN, M.D.

RANSOHOFF, J. LOUIS, M.D., F.A.C.S.
RANSOHOFF, JOSEPH, M.D., F.A.C.S.
RISLEY, EDWARD HAMMOND, M.D., F.A.C.S.
RITCHIE, HARRY P., M.D., F.A.C.S.
RODMAN, J. STEWART, M.D.
RODMAN, WILLIAM L., M.D.

SCHIFFBAUER, H., M.D. F.A.C.S.
SCHMIDT, ERWIN R., B.A., M.D.
SCHMITZ, HENRY, M.D., F.A.C.S.
SHAMBAUGH, GEORGE E., M.D.
SHERMAN, HARRY M., M.D.
SMITHIES, FRANK, M.D., F.A.C.P.
SOUTTER, ROBERT, A.B., M.D.
STANTON, E. MACD., M.D., F.A.C.S.
STURM, MEYER J., B.S.

TINKER, MARTIN B., M.D.

WEISENBURG, THEODORE H., M.D.

PUBLIC HEALTH AND HYGIENE

By Eminent Authorities

Edited by WILLIAM HALLOCK PARK, M.D.

Professor of Bacteriology and Hygiene, University and Bellevue Hospital Medical College; Director of the Bureau of Laboratories, Department of Health, New York City

Octavo, 884 pages with 123 illustrations. Cloth, $10.00, net

THE growing opinion that **public health is to a large extent purchasable** has stimulated health authorities to develop their opportunities and to assume greater responsibilities. The best medical colleges no longer confine their teaching to the diagnosis and treatment of disease, but give thorough courses in hygiene, and its practical application in preventive medicine. The technological schools are providing similar courses.

The great advances in hygiene and the increasing scope of public health work have led to the creation of many subdivisions and the problems and practices connected with these have become so highly technical as to require public health workers to restrict their activities to special lines. The medical officer for some time has appreciated this. Wherever the community is large enough to afford it, he has obtained **the service of specialists.** The department of health of any progressive State or large city has under the administrative head a number of bureaus, each of these under some specialist who has demonstrated his fitness.

The time has passed when any one person can possess the technical knowledge and personal experience required properly to direct and develop all or even several of these different branches of public health work. There was need **of a volume in which the most important phases of hygiene in relation to public health would be presented in a practical way by specialists actually devoting themselves to the subjects treated by them.** This book is intended for public health officials, physicians and medical students, and each contributor has therefore made his section as practical as possible and utilized to the full his own personal experience.

CONTENTS

Relation of Microörganisms to Disease, Wm. H. Park, M.D.

Antimicrobal or Antiprotein Substances Individually Considered, Wm. H. Park, M.D., and Charles Krumwiede, M.D., Assistant Director of the Bureau of Laboratories, New York City.

Prevention of Individual Infectious Diseases, Wm. H. Park, M.D.

Practical Use of Disinfectants, Wm. H. Park, M.D.

Epidemiology, Geo. A. Soper, Ph.D., Major, Sanitary Corps, U. S. A.

Sanitary Surveys, W. L. Dodd, Assistant Director, Department of Sanitation of the Pease Laboratories, N. Y.

Air and Health—Ventilation, C. E. A. Winslow, Dr. P. H., Professor of Public Health, Yale School of Medicine.

Housing, Lawrence Veiller, Secretary of the National Housing Association, N. Y.

Food, Edward K. Dunham, M.D., Lt.-Col., Medical Corps, U. S. A.

Vitamines, Alfred F. Hess, M.D., Clinical Professor of Pediatrics, New York University and Bellevue Hospital Medical College.

The Preservation and Adulteration of Food, J. P. Atkinson, M.S., Chief Chemist, Department of Health, N. Y.

Bacterial and Other Contaminations of Milk, Their Relation to Public Health, Wm. H. Park, M.D.

Bacterial Infections and Parasitic Diseases from Milk, Meat and Other Foods, Wm. H. Park, M.D.

The Soil, Arthur R. Guerard, M.D., Lecturer on Social Hygiene, New York State Department of Health.

Water Supplies and Their Purification. James T-B. Bowles, B.S., Lecturer in Water Supply and Sewage Disposal, New York University, Department of Hygiene, Bellevue Hospital Medical College; formerly in charge of Water Supplies and Purification Plants, Canal Zone, Panama.

Sewage and Waste Disposal, James T-B. Bowles, B.S.

Housing and Plumbing, Arthur R. Guerard, M.D.

The Sanitation of Swimming Pools. Wallace A. Manheimer, Ph.D., Vice-President of the International Congress on Public Baths, Belgium, 1920.

Personal Hygiene, Eugene Lyman Fisk, M.D., Medical Director of the Life Extension Institute, New York.

Additional Practical Points in Personal Hygiene, Arthur R. Guerard, M.D.

Military Hygiene, C. W. Berry, M.D., Lecturer on Military Hygiene, New York University and Bellevue Medical College, Brigadier-General, N. Y. National Guard.

Rural Public Health Work, Frank Overton, M.D., P.H., Sc.C., Sanitary Supervisor, N. Y. State Dept. of Health.

Tropical Hygiene, M. F. Connor, M.D., Health Officer, Panama Canal, 1904–1914; Senior State Director, International Health Board.

Industrial Hygiene, Louis I. Harris, M.D., Director of Bureau of Preventable Diseases, N. Y. City; Medical Advisor to the Labor Sanitation Conference, Greater New York.

Child Hygiene, S. Josephine Baker, M.D., D.P.H., Director of Bureau of Child Hygiene, Department of Health, New York; Consultant in Child Hygiene, U. S. Public Health Service.

Sociologic and Economic Aspects of Disease, Charles F. Bolduan, M.D., Chief of the Section of Public Health Education, U. S. Public Health Service.

Public Health Education, Charles F. Bolduan, M.D.

Mental Hygiene, August Hoch, M.D., late Director, Psychiatric Institute, Manhattan State Hospital for the Insane, New York.

Mental Defectives, Preventing and Controlling Measures, Henry H. Goddard, Ph.D., Director of Bureau of Juvenile Research, Columbia, O.

Maritime Quarantine, Leland E. Cofer, M.D., Health Officer of the Port of New York.

Vital Statistics, William H. Guilfoy, M.D., Registrar of Records, Department of Health, New York and Shirley W. Wynne, M.D., Chief of Division of Statistical Research, Department of Health, New York.

706-8-10 Sansom St. PHILADELPHIA

LEA & FEBIGER

PUBLISHERS

2 W. 45th Street NEW YORK

THE BATTLE CREEK SANITARIUM AND HOSPITAL

Established 1866

MEDICAL OBSTETRICAL ORTHOPEDIC
NEUROLOGICAL SURGICAL RECONSTRUCTIVE

EDUCATIONAL DEPARTMENTS

Training School for Nurses Normal School of Physical Education
School of Home Economics and Dietetics

Students received on favorable terms. Registered trained nurses, dietitians and physical directors supplied.

DESCRIPTIVE LITERATURE MAILED FREE UPON REQUEST

THE BATTLE CREEK SANITARIUM
BATTLE CREEK Box 247 MICHIGAN

To stabilize the alkaline reserve

in the acute infections (including influenza and pneumonia) large quantities of alkali are needed.

If their administration offers difficulty

PRESCRIBE KALAK WATER

Each bottle carries in sparkling form several grammes of the bicarbonates of sodium, potassium, calcium and magnesium.

Kalak Water Company of N.Y.
23 City Hall Place New York City

HEMORRHOIDS FISSURE FISTULA

IN practically every case of hemorrhoids, fissure, fistula, proctitis, prostatitis, etc., there is a history of constipation. One primary indication for treatment is to maintain free, easy bowel movements without straining.

Nujol is the ideal agent for such purpose. It promotes peristalsis by softening, moistening and lubricating the feces. It is an emollient that protects and soothes irritated and inflamed mucus.

Nujol brings about and maintains regular, easy bowel movements. Can be given for any length of time in any dose required.

Nujol

REG. U.S. PAT. OFF.

Nujol Laboratories, Standard Oil Co. (New Jersey), Room 788, 44 Beaver Street, New York City.

Please send me booklet "The Treatment of Hemorrhoids", and sample of Nujol.

Name .....

Address .....

VOL.

182

A
T

THE
EFFE
PROB
EXPE
PULM
STU
EMP
A R
SACC
SILV
INDE

Phi

COPYR